Thesis for the degree of Doctor of Philosophy

Towards Natural Control of Artificial Limbs

A Novel Osseointegrated Human-Machine Gateway, Neuromuscular Electrodes, and Pattern Recognition

by

Max J. Ortiz Catalán

Division of Signal Processing and Biomedical Engineering
Department of Signals and Systems
CHALMERS UNIVERSITY OF TECHNOLOGY

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Division of Signal Processing and Biomedical Engineering
Department of Signals and Systems
Chalmers University of Technology
SE-412 96, Gothenburg, Sweden.
e-mail: maxo@chalmers.se
e-mail: max_jair@hotmail.com

Faculty opponent:
Prof. Todd Kuiken, M.D., Ph.D.,
Center for Bionic Medicine, Rehabilitation Institute of Chicago, and
Feinberg School of Medicine, Northwestern University,
Chicago, United States of America.

Cover:
Illustration of intuitive prosthetic control and sensory feedback via physiologically appropriate neural pathways. The mechanical coupling and communication between the artificial limb and the human body is enabled via an osseointegrated implant.

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To whom it may concern...

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Abstract

The use of implantable electrodes has been long thought as the solution for a more natural control of artificial limbs, as these offer access to long-term stable and physiologically appropriate sources of control, as well as the possibility to elicit appropriate sensory feedback via neurostimulation. Although these ideas have been explored since the 1960's, the lack of a long-term stable human-machine interface has prevented the utilization of even the simplest implanted electrodes in clinically viable limb prostheses.

In this thesis, a novel human-machine interface for bidirectional communication between implanted electrodes and the artificial limb was developed and clinically implemented. The long-term stability was achieved via osseointegration, which has been shown to provide stable skeletal attachment. By enhancing this technology as a communication gateway, the longest clinical implementation of prosthetic control sourced by implanted electrodes has been achieved, as well as the first in modern times. The first recipient has used it uninterruptedly in daily and professional activities for over one year. Prosthetic control was found to improve in resolution while requiring less muscular effort, as well as to be resilient to motion artifacts, limb position, and environmental conditions.

In order to support this work, the literature was reviewed in search of reliable and safe neuromuscular electrodes that could be immediately used in humans. Additional work was conducted to improve the signal-to-noise ratio and increase the amount of information retrievable from extraneural recordings. Different signal processing and pattern recognition algorithms were investigated and further developed towards real-time and simultaneous prediction of limb movements. These algorithms were used to demonstrate that higher functionality could be restored by intuitive control of distal joints, and that such control remains viable over time when using epimysial electrodes. Lastly, the long-term viability of direct nerve stimulation to produce intuitive sensory feedback was also demonstrated.

The possibility to permanently and reliably access implanted electrodes, thus making them viable for prosthetic control, is potentially the main contribution of this work. Furthermore, the opportunity to chronically record and stimulate the neuromuscular system offers new venues for the prediction of complex limb motions and increased understanding of somatosensory perception. Therefore, the technology developed here, combining stable attachment with permanent and reliable human-machine communication, is considered by the author as a critical step towards more functional artificial limbs.

Keywords: advanced prosthetic control, artificial limbs, bone-anchored prostheses, cuff electrodes, epimysial electrodes, neural interfaces, neurostimulation, osseointegration, pattern recognition, real-time and simultaneous prosthetic control, robotic prostheses, sensory feedback.

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"*If I have seen further, it is only by standing on the shoulder of giants*"

\- Sir Isaac Newtown

List of Publications

This doctoral thesis is based on the work contained in the following publications referred by Roman numerals in the text.

I. ***Ortiz-Catalan, M.,*** Brånemark, R., Håkansson, B., and Delbeke, J., **On the viability of implantable electrodes for the natural control of artificial limbs: Review and discussion**, *Biomedical Engineering Online*, 2012, 11:33 - *'Highly accessed'*.

II. ***Ortiz-Catalan, M.,*** Marin-Millan, J., Delbeke, J., Håkansson, B., and Brånemark, R., **Effect on signal-to-noise ratio of splitting the continuous contacts of cuff electrodes into smaller recording areas**, *Journal of Neuroengineering Rehabilitation*, 2013, 10:20.

III. ***Ortiz-Catalan, M.,*** Brånemark, R., and Håkansson, B., **BioPatRec: A modular research platform for the control of artificial limbs based on pattern recognition algorithms**, *Code Source for Medicine and Biology*, 2013, 8:11.

IV. ***Ortiz-Catalan, M.,*** Håkansson, B., and Brånemark, R., **Real-time and simultaneous control of artificial limbs based on pattern recognition algorithms**, *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, in press - advance online publication DIO: 10.1109/ TNSRE.2014.2305097.

V. ***Ortiz-Catalan, M.,*** Håkansson, B., and Brånemark, R., **Osseointegrated human-machine gateway for long-term stable sensory feedback and motor control of artificial limbs**, *under review* at *Science Translational Medicine.*

Other relevant publications by the author that are not included as part of this doctoral thesis.

- ***Ortiz-Catalan, M.,*** Sander, N., Kristoffersen, M., Håkansson, B., and Brånemark, R., **Treatment of phantom limb pain (PLP) based on augmented reality and gaming controlled by myoelectric pattern recognition: a case study of a chronic PLP patient**, *Frontiers in Neuroscience*, 2014, 8:24

- ***Ortiz-Catalan, M.,*** Brånemark, R., and Håkansson, B., **Evaluation of classifier topologies for the real-time classification of simultaneous limb motions**, in *Proceedings of the 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC).* Osaka, Jul. 3-7, 2013.

- ***Ortiz-Catalan, M.,*** Håkansson, B., and Brånemark, R., **Real-time classification of simultaneous hand and wrist motions using Artificial Neural Networks with variable threshold outputs**, in *Proceedings of the XXXIV International Conference on Artificial Neural Networks (ICANN),* Amsterdam, May 15-16, 2013, 77:1159-1164.

- ***Ortiz-Catalan, M.,*** Brånemark, R., and Håkansson, B., **Biologically inspired algorithms applied to prosthetic control**, in *Proceedings of the IASTED International Conference, Biomedical Engineering.* Innsbruck, Feb. 15-17, 2012:7-15.

- Khong, L., Gale, T.J., Jiang, D., Oliver, J.C., and ***Ortiz-Catalan, M***. **Multi-layer perceptron training algorithms for pattern recognition of myoelectric signals**, in *Proceedings of the Biomedical Engineering International Conference (BMEiCON),* Krabi, Oct. 23-25, 2013.

- ***Ortiz-Catalan, M.,*** Nijenhuis, S., Ambrosh, K., Bovend'Eerdt, T., Koenig, S., and Lange, B., **Virtual Reality**, in *Emerging Therapies in Neurorehabilitation,* Biosystems & Biorobotics Vol. 4, Edit. Pons, J.L., and Torricelli, D., Springer-Verlag, 2014.

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Acronyms

ALC	Artificial limb controller
ANN	Artificial neural network
BMI	Brain-machine interface
CNS	Central nervous system
DoF	Degrees of freedom
EMG	Electromyography
HD-sEMG	High-density surface electromyography
IC	Integrated circuit
IMES	Implantable myoelectric sensors
LDA	Linear discriminant analysis
MES	Myoelectric signals
MLP	Multi-layer perceptron
MPR	Myoelectric pattern recognition
OHMG	Osseointegrated human-machine gateway
OPRA	Osseointegrated prosthesis for the rehabilitation of amputees
PCA	Principal component analysis
PNS	Peripheral nervous system
PRA	Pattern recognition algorithm
SCI	Spinal cord injury
sEMG	Surface electromyography
SNR	Signal-to-noise ratio
TAC	Target achievement control
TMR	Targeted muscle reinnervation

Thesis Framework

Introduction

Scope of the Thesis

As opposed to axolotls that can regenerate their limbs and tails (Figure 1), or the planarian flatworm that goes as far as regenerating its head and body from only its tail, humans do not have such remarkable capabilities of recovering after an amputation. Despite recent advancement in regenerative medicine, such as the finding that blocking the *Wnt* signaling pathway[1] (common through the animal kingdom) allows species of flatworms with limited generation capabilities to grow severed heads (Sikes and Newmark, 2013), the translation of such discoveries into humans regenerating amputated limbs, is today extremely futuristic.

Figure 1. Limb regeneration by an axolotl[2]

Analogous to solid organ transplantation, a limb can be transplanted in a surgical procedure as a treatment for limb amputation. This is currently a rare procedure (approximately 70 cases worldwide), and it is contraindicated for unilateral and congenital amputees (Elliott *et al.*, 2013). Arguments for limb transplantation include cosmetic restoration, certain degree of intuitive motor control, and limited but naturally perceived sensory feedback. Current drawbacks include shortened expected life span (due to lifelong immunosuppression), potential rejection and its treatment, and high costs. Because of these reasons, hand transplantation has been mainly performed in bilateral amputees, as the tradeoff between benefits and drawbacks in unilateral and above-elbow amputations is more difficult to balance.

This doctoral thesis is dedicated to artificial limbs, or limb prostheses, as currently being the most common method used for limb replacement. More specifically, this work deals with

[1] Means of cellular communication considered important for cell proliferation and differentiation.

[2] Image by James Monaghan used with permission, http://nuweb5.neu.edu/monaghanlab/, accessed Jan 1st, 2014.

the control of powered upper limb prostheses, rather than the prosthetic hardware itself. The approach employed in this work addresses three of the major problems in the field, namely:

1. The mechanically stable attachment of the limb prosthesis to the stump. This is addressed via orthopedic osseointegration as the mean to provide direct skeletal attachment, and further enhanced as a communication interface (Paper V).

2. The lack and instability of physiologically appropriate signals to intuitively control several degrees of freedom of the prosthetic limb. This is approached by implanted neuromuscular interfaces (Papers I and II) and decoding algorithms (Papers III and IV).

3. The lack of appropriate and distally referred sensory feedback. This is addressed by implanted neural interfaces (Papers I and II) and neurostimulation (Paper V).

Neuromuscular interfaces in the context of this thesis refer to electrodes at the peripheral nerves and muscles, excluding the central nervous system (brain-machine interfaces [BMIs]).

Aims of the Thesis

The purpose of this doctoral thesis is to improve the control of powered limb prostheses by enabling the clinical use of implantable neuromuscular interfaces. In order to achieve this, the principal objective is to develop a long-term stable and bidirectional osseointegrated human-machine gateway (OHMG), which allows for the communication between the implanted neuromuscular electrodes and the artificial limb (Figure 2).

The direct connection to the neuromuscular system as the source of control is required for the OHMG to be clinically useful. Therefore another objective of this work is to investigate the viability of current neuromuscular electrodes for the control of artificial limbs, as well as to further develop them if necessary.

The third objective of this thesis is to investigate advanced prosthetic control strategies based on pattern recognition algorithms. This is with the purpose to allow for intuitive control of additional degrees of freedom (DoF) than currently possible by conventional myoelectric control.

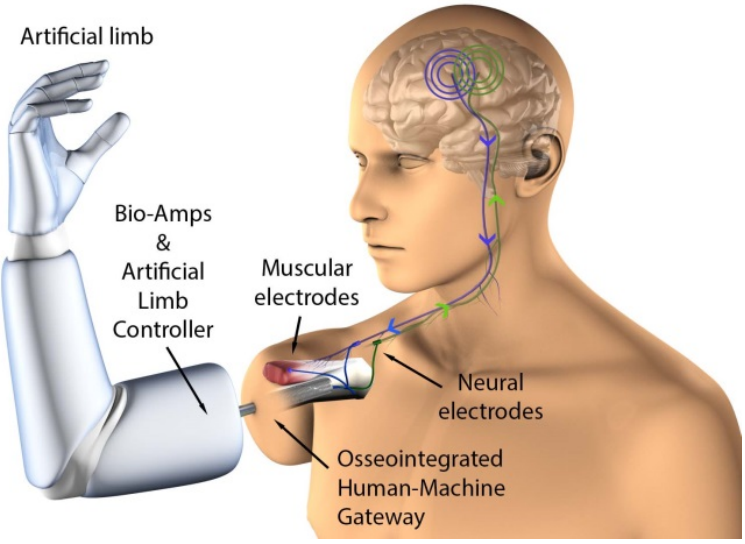

Figure 2. The Osseointegrated Human-Machine Gateway (OHMG), a long-term and bidirectional communication interface between neuromuscular electrodes and the artificial limb.

Motivation

Approximately 1,000 to 1,100 amputations have been estimated to occur every year in Sweden (Johannesson, 2009). In the United States of America, a 1.6 million amputee population was estimated in 2005, and this number is expected to double in 2050 (Ziegler-Graham *et al.*, 2008). In both countries, lower limb amputation is the most common (Pezzin *et al.*, 2000, 2004; Dudek *et al.*, 2005; Asplund *et al.*, 2009), and cardiovascular diseases the most common cause (Johannesson, 2009; Adams *et al.*, 1999), while traumatic amputations are most common in younger people (Pezzin *et al.*, 2000; Asplund *et al.*, 2009). In Sweden, the incident for traumatic amputations was observed to be 5.21 per 100,000 person-year between 1998 and 2006, with males between 15 and 30 years of age suffering most of the traumatic amputations (Asplund *et al.*, 2009).

The *International Classification of Functioning, Disability and Health* (ICF), by the *World Health Organization* (WHO), classifies disabilities at three levels: 1) body functions and structures, 2) activity, and 3) participation (WHO, 2002). The loss of an extremity has a clear impact in all of them at different degree depending on the amputation level.

An integral rehabilitation is crucial for the quality of independent living after a traumatic event such as a limb amputation, especially in young and active patients with high mobility requirements. Analogously, patients with congenital malformation face similar challenges to alleviate what otherwise are life-permanent disabilities. A successful limb replacement would not only improve the patient's quality of life, but also facilitate the individual integration as a productive member of the society. Additional benefits that must not be overlooked are the reduced burden placed on the patient's family, and the improvement of their social relationships. Additionally, restoring the functionality of a missing limb will also impact the social cost associated to these disabilities, which is relevant to current worldwide concerns on the burden of healthcare expenses.

A Brief History on Robotic Prostheses

The use of cosmetic and potentially functional prosthetic devices is estimated as long back as 950-750 BCE[3] (Finch *et al.*, 2012). Several improvements in prosthetic technology involving a wide variety of disciplines have been reported since then. The following is a non-exhaustive compilation of findings and achievements relevant to powered upper limb prosthetics, and the quest for mastering their control.

1948 Demonstration of myoelectric control (Reiter, 1948).

1959 Discovery of osseointegration by P.I. Brånemark (Brånemark, 1959).

1960's Myoelectric prosthesis clinically implemented in Europe and Russia (Sherman, 1964). Electromagnetic noise was early recognized as a major problem.

1964 Probably the first attempt of hand transplantation in a bilateral amputee. It failed and resulted in re-amputation three weeks later (Gilbert, 1964; Elliott *et al.*, 2013).

1967 Utilization of myoelectric pattern recognition (MPR) to decode motor intention from synergistic muscle activations recorded by surface electrodes (Finley and Wirta, 1967).

1968 Fully implanted myoelectric recording electrodes using telemetry (Herberts *et al.*, 1968). Five out of six devices were removed owing to mostly mechanical failures (3 to 15 months implantation). The implant distance to the skin surface was observed as critical.

1970's Implanted neurostimulators to treat chronic pain with follow up for over 9 years (Nashold *et al.*, 1982), and to correct footdrop (Waters *et al.*, 1975) with follow up for over 12 years (Waters *et al.*, 1985). Both systems used cuff electrodes as a neural interface and were probably the first long-term implanted neurostimulators.

1973 Myoelectric pattern recognition using surface electrodes at the stump (Herberts *et al.*, 1973; Graupe *et al.*, 1973). Simultaneous control was reported without a quantitative evaluation (Herberts *et al.*, 1973). Although analog electronics were

[3] before common era

used by Herberts *et al.*, microprocessors were argued to be already sufficient to compute classification in real-time by Graupe (1974).

1974 Peripheral nerve stimulation provided sensory feedback to patients wearing body-powered prostheses. A series of patients were treated with a fully implanted system enabled with telemetry (Clippinger *et al.*, 1974). The causes that prevented the continuation of this work are unknown to the author (no further reports were found). Duke University and Avery Laboratories did not answer on the author requests of further information.

1977 Implantation of epimysial and cuff electrodes intended for prosthetic control in an amputee (Stein *et al.*, 1980; Hoffer and Loeb, 1980). Improved controllability was reported until the implementation had to be stopped due to infection in the percutaneous lead. No motor activity was recorded with the cuff electrode, however, stimulation was possible.

1977 Direct simultaneous control using epimysial electrodes (2 DoF); *one-for-one* (*one-electrode to one-action*) (Stein *et al.*, 1980; Hoffer and Loeb, 1980).

1977 Study on the discrimination of artificially inputted feedback information using neurostimulation (Anani *et al.*, 1977).

1978 Clinical trials of prosthetic control based on myoelectric pattern recognition within a laboratory environment (Herberts *et al.*, 1978; Wirta *et al.*, 1978). Analog electronics implemented the classifiers and were embedded in a transradial prosthesis capable of 6 movements. Real-time tests for MPR controllers were introduced (Herberts *et al.*, 1978). An independent study employed the synergistic activation of more proximal muscles for the control of transhumeral prostheses, however hand open/close was not decoded (Wirta *et al.*, 1978).

1979 Home clinical trial of prosthetic control based on myoelectric pattern recognition and surface electrodes (Almström *et al.*, 1981).

1980 Hoffer & Loeb suggested the possibility to use remnant muscles as biological amplifiers of neuroelectric signals physiologically corresponding to the lost degrees of freedom (principle of *targeted muscle reinnvervation*, Hoffer and Loeb [1980]).

1981 Prosthetic sensory feedback through neurostimulation in lower limb amputees using telemetry (Clippinger *et al.*, 1981). Similar technology as mentioned above in year 1974 (Clippinger *et al.*, 1974).

1981 Microneurography report of potential motor neural activity in long-term amputees (< 4 years, Nyström and Hagbarth [1981]).

1982 Feasibility experiment to record motor neural activity from the ulnar, median and radial nerves in an amputee using wire loops as extraneural electrodes (De Luca *et al.*, 1982).

1990 Orthopaedic osseointegration allowed the first long-term successful bone-anchored limb prostheses (Brånemark *et al.*, 2001).

1998 Technically successful hand transplantation (Dubernard *et al.*, 1999). The transplanted hand was eventually amputated presumably because the patient was unable to physiologically adapt to the donor's hand (Elliott *et al.*, 2013).

2000 Real-time and simultaneous control of a robotic arm using brain-machine interfaces in non-human primates (Wessberg *et al.*, 2000).

2004 First patient treated with Targeted Muscle Reinnvervation (TMR). Muscles that no longer act over a joint, and thus have no functional actuation, were reinnervated with nerve branches from lost distal muscles. This allowed for direct simultaneous control (*one-for-one*) of 2 DoF using surface electrodes (Kuiken *et al.*, 2004).

2004 Study suggests the feasibility of recording neural motor activity from long-term amputees (up to 15 years) using short-term implanted intrafascicular electrodes. Moreover, these electrodes were also used to elicit discrete and graded sensations of touch and joint position/movement (Dhillon *et al.*, 2004, 2005).

2005 Demonstration of direct prosthetic control and sensory feedback using intrafascicular electrodes (short-term implantation) in long-term amputees (Dhillon and Horch, 2005).

2010 Decoding of motion intent (3 movements) using intrafascicular electrodes (short-term implantation) in a transradial amputee (Micera *et al.*, 2010).

2011 Object discrimination through solely direct stimulation of afferent fibers using short-term implanted intrafascicular electrodes in amputees (Horch *et al.*, 2011).

2012 Real-time, proportional, and simultaneous control of a robotic arm by a patient with tetraplegia via a brain-machine interface consisting of 2 microelectrode arrays (Collinger *et al.*, 2012). Experiments conducted in a controlled environment (patient does not use it at home).

2013 Demonstration of long-term reproducibility of sensory perception through neurostimulation in patients at 18 months (Tan *et al.*, 2013) and 10 years (Paper V) after amputation.

2013 Permanent and bidirectional communication between implanted electrodes and artificial limbs enabled via an osseointegrated implant (Paper V). This allowed for probably the first (in modern times since 1977 [Stein *et al.*, 1980; Hoffer and Loeb, 1980]), and longest implementation of prosthetic control sourced by implanted neuromuscular interfaces in daily and professional activities (> 1 year).

2013 A transradial amputee was the first recipient of the implantable myoelectric sensors (IMES [Weir *et al.*, 2009]). These are fully implantable and wireless intramuscular recording electrodes designed for prosthetic control (as in Herberts *et al.* [1968]), and probably the first wireless solution used by patients in activities of the daily living in modern times (Pasquina *et al.*, under review).

Current Clinical Situation

Attention must be paid when the literature indicates that certain technologies have allowed disable patients to performed *activities of daily living*, as this suggests that the disability in question have been reduced or overcome. However, the conditions in which such improvements have been demonstrated must be carefully assessed. More often than not, the technologies in question have proven their principle within the convenience of research laboratories, and in a short period of time, which does not necessarily mean readiness for clinical dissemination. This is unfortunately the case for artificial limbs (Jiang *et al.*, 2012a; Farina *et al.*, 2014), and to less extent for neuroprostheses (Borton *et al.*, 2013b).

Prosthetics have been thought as "*the oldest of the technological rehabilitation sciences*" (Andrade *et al.*, 2014), and although bionic limb replacement with neuromuscular control was devised since the 1940's (Reiter, 1948), artificial limbs are still far from providing the functionality of their biological counterpart. Moreover, technology used since the 1960's is still the *state-of-the-art* solution provided to patients in clinics around the world. Myoelectric prosthesis using surface electrodes with control strategies established decades ago, such as "*two-site two-states*" or "*one-site three-states*" (Parker and Scott, 1986; Parker *et al.*, 2004), are presently the most sophisticated solutions available to patients. An exception to the latter are subjects treated with Targeted Muscle Reinnervation (TMR, Kuiken *et al.*, 2004), a surgical procedure that allows for additional myoelectric sites for *direct control* ("*one-site one-action*" or "*one-for-one*" [Wirta *et al.*, 1978]). However, TMR patients continue to suffer from the challenges presented by surface electrodes (Schultz and Kuiken, 2011), a technology plagued with instability problems (Paper I), to the point where the persistence of noise in surface recordings has been described as "endemic and unavoidable" (De Luca *et al.*, 2010).

The introduction of osseointegration to provide stable mechanical attachment of prosthetic limbs to the skeleton has shown to improve quality of life for amputees (Brånemark *et al.*, 2014). However, as a coupling mechanism alone, it mostly affects the functionality of joints adjacent to the amputation. The control of a powered terminal device, or other more distal joints, has continued to depend mostly on superficial myoelectric recordings.

Functionality was early identified as the main need in upper limb prosthesis (LeBlanc, 1985). Currently, there are commercially available robotic devices to substitute elbow, wrist, and hand with individually actuated fingers, which could potentially restore considerably more functionality than a single actuated unit. However, since patients can hardly control more than one of these units at the time, these powered prosthetic devices are rarely used all together (elbow + wrist rotator + hand) and to their full capabilities (finger control in high-end hand prostheses). Moreover, no tactile feedback is currently provided, even in its simplest form (Antfolk *et al.*, 2013). This is despite that sensing hardware (position and force sensors) is widely available for robotic applications. All this might explain why despite that more advanced prosthetic hardware has been made available in the last decades, improved functionality continues to be requested by patients using powered upper limb prosthesis (Kyberd *et al.*, 2007).

Now that prosthetic hardware is potentially capable to restore considerable more functionality, the major challenge in the field is widely recognized to be to produce reliable and intuitive control (Atkins *et al.*, 1996; Hargrove *et al.*, 2010; Cipriani *et al.*, 2011; Pistohl *et al.*, 2013; Andrade *et al.*, 2014), which is mainly limited due to the lack of long-term stable and physiologically appropriate control signals (Baker *et al.*, 2010; Scheme and Englehart, 2011). Inherent to amputation, some or all of the muscles required for actuation are lost, thus causing a lack of myoelectric signals suitable for advanced prosthetic control. Paradoxically, as the level of amputation increases, more functions need to be restored while fewer myoelectric control sites are left available to do so (Hoffer and Loeb, 1980). Furthermore, the environmental dependency of surface electrodes can only deliver temporarily stable signals, which have shown to be insufficient for clinical implementations of control strategies beyond *direct control* (Schultz and Kuiken, 2011).

Conversely, implantable electrodes have the potential of providing additional, long-term stable, and physiologically appropriate control signals, as well as to elicit appropriate and distally referred sensory feedback (Paper I). However, the problem of achieving permanent electrode-prosthesis communication, due to the lack of a reliable and long-term stable cutaneous interface, has been a major obstacle for the utilization of implanted electrodes beyond research experiments. To find a solution to this long-standing problem is the main focus of this thesis (Paper V). The sources for control (Paper I, II) and pattern recognition strategies to improve controllability are also addressed (Paper III, IV).

Myoelectric pattern recognition (MPR) has shown promising results for the intuitive control of several prosthetic units when evaluated in controlled environments. However, it has still not produced clinical evidence of its practical usability (Andrade *et al.*, 2014), despite being tested in clinical trials since the 1970's (Herberts *et al.*, 1978; Wirta *et al.*, 1978; Almström *et al.*, 1981). A major limitation recognized back then, and which continues today, is precisely the instability of surface electrodes. The variability resulting from the use of surface electrodes are known to be detrimental to the prediction of motion intent (Tkach *et al.*, 2010). Epimysial electrodes, as the implanted analogous of surface electrodes, could provide the missing stability required for MPR implementation, but again, neither *direct control* nor MPR systems have been able to clinically exploit the advantages of even the simplest implanted electrodes due to the lack of a reliable and long-term stable human-machine communication.

Summary of the current clinical situation:

- Prosthetic hardware and decoding technology are currently available to potentially improve the functionality of limb prostheses.
- However, the lack of sufficient, long-term stable, and physiologically appropriate control signals have hindered the clinical utilization of such hardware and decoders.
- Implantable electrodes can provide long-term stability and additional physiologically appropriate control signals, furthermore, neural interfaces can be used to provide intuitive and appropriate sensory feedback.
- However, implantable electrodes have not been clinically used due to the lack of a long-term stable and reliable human-machine trans/percutaneous interface.

Neuroprosthetics

Neuroprostheses aim to restore a certain degree of sensorimotor impairments (Hoffer *et al.*, 1996; Borton *et al.*, 2013b). In the case of spinal cord injuries (SCI), where the volitional control of muscles is lost, a fully implantable system can be used to record control signals from more proximal and still voluntarily controlled muscles in order to stimulate those impaired (Figure 3). Such systems have been clinically tested in humans for over 2 years in activities of daily living (Kilgore *et al.*, 2008). Its predecessor, the FreeHand System, was probably the first commercial neuroprosthesis for restoring upper limb motion in SCI (Peckham *et al.*, 2001), and it has been estimated that 250 patients have been recipients worldwide (Kilgore *et al.*, 2008). The obvious difference between neuroprostheses and limb prostheses is that since the biological actuators are lost in the latter, hence new requirements on the mechanical and communication interface arise. Nevertheless, the knowledge gained by neuroprostheses in materials, leads, connectors, and electrode technology, have been instrumental for the work realized in this doctoral thesis.

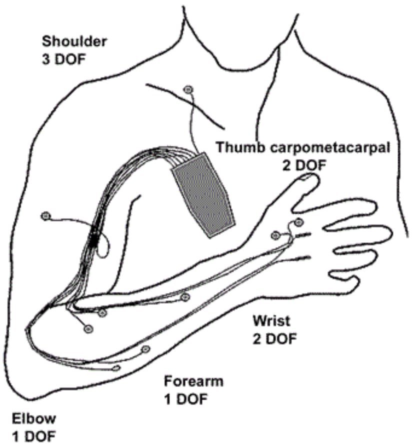

Figure 3. Illustration of a fully implanted neuroprosthesis aimed to restore upper limb function. Image published in the open access article: Kilgore *et al.* (2003).

Targeted Muscle Reinnervation (TMR)

Neural recordings represent several technological challenges due to the small amplitude of the nerve conducting action potentials (few μV). In 1980, Hoffer and Loeb suggested the reinnervation of available muscles with more functionally relevant nerve branches deprived from their original target muscle due to the amputation (Hoffer and Loeb, 1980). This idea was first brought to clinical reality by Kuiken *et al.* (2004) in a patient that suffered from a bilateral shoulder disarticulation. By increasing the number of myoelectric control sites (Figure 4), TMR allows for simultaneous control of myoelectric prosthesis (*one-for-one)* using surface electrodes. Furthermore, an additional and unexpected benefit of this procedure is that sensory fibers innervate skin patches in their new targets, thus providing naturally perceived sensory feedback (Kuiken *et al.*, 2007a, 2007b). It has been estimated that over 60 patients have been treated with this procedure since 2002 (Young *et al.*, 2014). Presently, no study has been published on the efficacy of this technique.

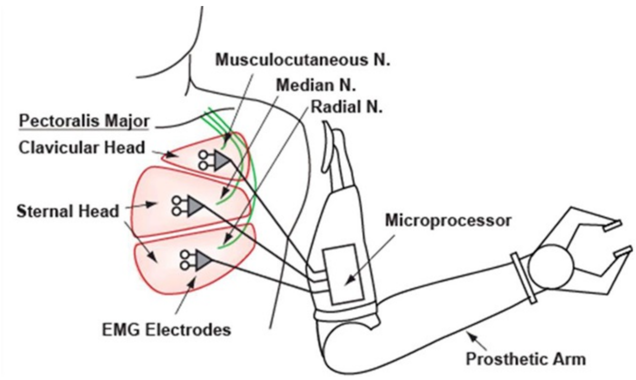

Figure 4. Illustration of the Targeted Muscle Reinnervation (TMR) procedure in a patient with shoulder disarticulation in which the musculocutaneous, median, and radial nerves were used to reinnervate the pectoralis major muscle, and thus provide myoelectric sites for intuitive prosthetic control. Illustration by the Rehabilitation Institute of Chicago and published in the open access article: Scheme and Englehart (2011).

Recently, another surgical technique has been proposed in which a small portion of muscle is transplanted to serve as a target for nerves severed by the amputation (Kung *et al.*, 2013a, 2014). As in TMR, these muscles do not aim to actuate over a joint, but serve as biological amplifiers for the neural motor commands. However, since the transplanted muscle is smaller than those used in TMR, surface electrodes might be unable to capture its electrical activity. This technology named Regenerative Peripheral Nerve Interface (RPNI) is therefore designed for implanted muscular electrodes. The idea has been currently tested using epimysial electrodes in animal models with promising results (Urbanchek *et al.*, 2011; Kung *et al.*, 2013b, 2014).

Prosthesis Attachment

Sockets

The conventional method to attach limb prostheses to the patient's stump is the use of a socket. Sockets rely on mechanically compressing the stump to secure the limb prosthesis, and therefore loads are transferred through the soft tissue by direct contact on the skin. Compression is a constant aggression to skin and soft tissue, which results in a variety of problems ranging from inconvenient to disabling. As a result, socket suspension is regarded as a major source of problems for amputees (Lyon *et al.*, 2000; Hagberg and Brånemark, 2001; Dudek *et al.*, 2005; Pezzin *et al.*, 2004; Gailey *et al.*, 2008).

The heavier the prosthesis, or the higher the loads developed during prosthetic use, the stronger will be the coupling required to keep the prosthesis in place. This translates into a higher compression and adhesion by the socket on the skin. For this reason, it is not surprising that the most active patients have an increased risk of dermatologic problems (Dudek *et al.*, 2005). However, this situation is not exclusively reported by the most active prosthetic users, problems such as dermatitis and infected sores are also commonly reported by amputees due to this coupling mechanism (Lyon *et al.*, 2000; Hagberg and Brånemark, 2001; Dillingham *et al.*, 2001; Dudek *et al.*, 2005; Pezzin *et al.*, 2004).

Heat transfers poorly between the skin and the socket (Andrade *et al.*, 2014), thus unavoidably causing discomfort. Physical activity and environmental conditions will cause increased heat and sweat within the socket interface (Hagberg and Brånemark, 2001), which also translates to unpleasant odors. The latter could affect the social relationships of the subjects at different levels depending on their cultural background.

The hard frame of a socket, inherently limits the range of motion when close to the joints. Moreover, patients with short stumps cannot use a socket without locking or reducing the range of motion of the adjacent joint, which results in increase disability at the functional level, and potentially at the activity and participation levels as well, for example: 1) patients with high bilateral transfemoral amputations can hardly use sockets that provide enough suspensions for the prosthetic legs, thus wheelchairs become their only option for mobility; 2) in a high transhumeral amputation, the socket or complementary suspension components cover part of the shoulder or chest, thus limiting its range of motion and causing additional discomfort (Figure 5). Moreover, even in cases where the adjacent joint is not locked, moving into certain limb position will cause friction between the socket and adjacent tissue, *e.g.*, sitting discomfort is commonly reported by patients with transfemoral amputations (Hagberg and Brånemark, 2001). Discomfort caused by the socket has been reported by the majority of amputees (Dillingham *et al.*, 2001), and it has also been found as the major aspect of dissatisfaction among prosthetic users (Pezzin *et al.*, 2004). In summary, it is not surprising that the socket suspension has been found as a common denominator in problems affecting amputees' quality of life (Hagberg and Brånemark, 2009).

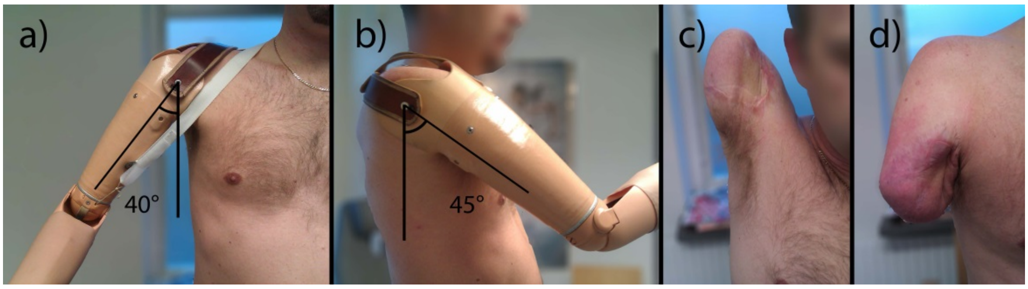

Figure 5. Example of a transhumeral amputee fitted with a socket prosthesis which limits shoulder abduction (a) and flexion (b) to less than 45°, despite that the patient is still capable of full range of motion (c). The distal part of the stump consists of approximately 40 mm of soft tissue which cannot be used to transfer load to the prosthesis, thus a harness is necessary to provide enough suspension (prosthetic fittings vary depending on the stump anatomy). Additionally, skin irritation can be observed at the stump due to the socket compression (d). Pictures by Stewe Jönsson adapted with permission.

Bone-Anchored Prostheses

Due to the inherent problems of socket suspension, the idea of a direct coupling between the artificial limb and the residual bone has been explored since decades ago (Mooney and Predecki, 1971). Aside to static biocompatibility, the materials for such surgical approach must allow living tissue to tolerate the functional stresses generated by prosthetic use. The failure of initial attempts to consolidate this idea has been attributed to the poor mechanical integration between bone and implant. The introduction of titanium solved this problem and allowed the first successful skeletal attachment of limb prostheses in 1990 (Brånemark *et al.*, 2001). This was based on the principle of *osseointegration* which was discovered by P.I. Brånemark in Gothenburg, Sweden, in the 1950's (Brånemark, 1959). Since then, research groups around the world have developed different bone-anchored systems (Pitkin, 2013).

Researchers at Gothenburg University, Sahlgrenska University Hospital, and Chalmers University of Technology have pioneered the use of osseointegration in a variety of applications since its discovery (Brånemark *et al.*, 2001); from dental implants (Brånemark *et al.*, 1977) to bone conducting devices to restore hearing impairment (Håkansson *et al.*, 1985; Snik *et al.*, 2005).

Based on the experience gathered with the first bone-anchored prostheses, R. Brånemark and colleagues established the Osseointegrated Prosthesis for the Rehabilitation of Amputees (OPRA) treatment protocol in 1999 (Hagberg and Brånemark, 2009), which has shown to provide stable and long-term fixation through radiostereometric analysis (Nebergall *et al.*, 2012). The Centre of Orthopaedic Osseointegration at the Department of Orthopaedics, Sahlgrenska University Hospital was established the same year to further develop the novel treatment concept (Figure 6). By the end of 2013, the Centre of Orthopaedic Osseointegration at Sahlgrenska University Hospital treated approximately 200 patients with osseointegrated limb prostheses (OPRA Implant System[4], Figure 7), of which the majority has been transfemoral amputations, but also transtibial, transhumeral, transradial and thumb amputations have been treated. Additionally, this treatment has been expanded to clinics around the world and it is currently provided in Australia, Belgium, Chile, Denmark, England, France, Netherlands, Portugal, and Spain.

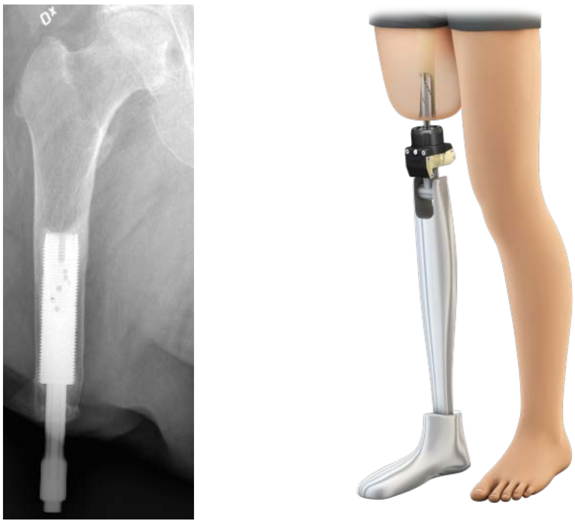

Figure 6. Five year follow up X-ray from a high transfemoral amputee treated with the OPRA protocol (left inset). Schematic illustration of a leg prosthesis couple to an osseointegrated implant via a safety device (right inset). The safety device prevents accidentally dangerous torque and bending movements to be transferred to the implant.

[4] Integrum, Gothenburg, Sweden.

The OPRA implant system has a modular design that has proven particularly useful for lower limbs where the abutment or abutment screw can bend or fracture before the bone is affected due to excessive mechanical stress, in which case these components are simply replaced in the out-patient clinic without the need of major surgery. In a recent study, 4 transfemoral patients (out of 51) required an abutment change due to such mechanical complications (2 year follow up). However, they immediately recovered normal function after replacing the damaged components (Brånemark *et al.*, 2014). The alternative bone-anchored implant designs will need to be completely removed in such situations, or would result in bone fracture, with either outcome requiring a long-recovery aside of potential hospitalization. Currently, no retrospective or prospective study has been published by other groups working with bone-anchored prostheses, and therefore the efficacy and complications of alternative designs are unknown.

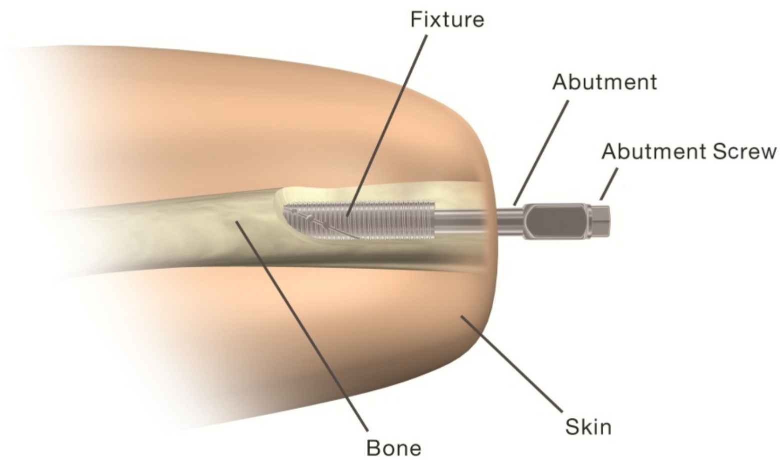

Figure 7. Illustration of the OPRA implant system. A fixture is implanted intramedullary and it becomes osseointegrated over time. An extension is created with the abutment which is the percutaneous component. Soft tissue is stabilized and fat is removed between the most distal part of the bone and the skin. This is done in order to reduce motion of the skin at the percutaneous interface.

There are inherent advantages of bone-anchored over socket suspension. The first and most obvious is the elimination of the socket itself, and thus the soft tissue compression, skin obstruction, limitation in the range of motion, and locking of adjacent joints. An additional advantage is the ease of donning and doffing (Figure 8), which has been found as an important consideration for patients (Kyberd *et al.*, 2007). Moreover, it has been found that OPRA patients use more sophisticated prosthesis, arguably because they can take better advantage of such devices when not afflicted by socket related problems (Häggström *et al.*, 2013a).

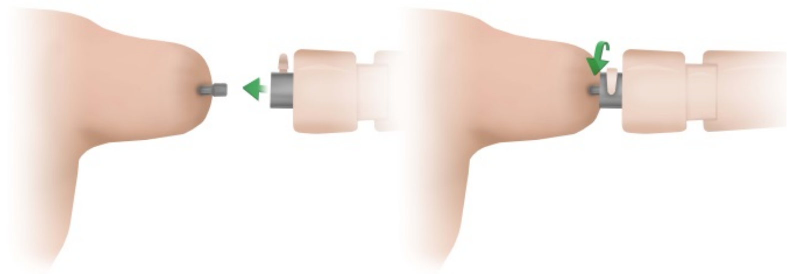

Figure 8. Donning and doffing of a bone-anchored transhumeral prosthesis using a clamp mechanism.

The Percutaneous Interface

A permanent percutaneous abutment is probably the most controversial part of bone-anchored prostheses. Percutaneous devices can present different failure modes (von Recum, 1984), from which the risk of infections is arguably the major concern, probably because this has been traditionally a problem of mechanically unstable percutaneous devices such as catheters and leads, but also for stable so called external fixator systems used for fracture treatment or callus distraction (*e.g.*, Ilizarov apparatus [Ilizarov, 1990]). Previous permanent percutaneous devices based on osseointegration faced an even stronger reluctance by professionals during their origins, particularly dental implants as the first clinical application in shifting the state-of-knowledge on implantable materials and percutaneous devices. Currently, a dental implant is a widely accepted technology which is routinely prescribed around the world. Another successful example of permanent osseointegrated devices are bone conducing hearing aids, for which a recent study found no adverse soft tissue reactions in 95.5% of 7,415 observations in 1,132 percutaneous implants (Dun *et al.*, 2012).

In the most recent study of the OPRA Implant System, no superficial infection was found to develop into a deep infection, and in average, patients had one superficial skin infection every other year, which were treated successfully with oral antibiotics (Brånemark *et al.*, 2014). Skin infections are commonly present due to socket suspension (Lyon *et al.*, 2000; Dudek *et al.*, 2005), and thus this is not a problem exclusively of bone-anchored prostheses. In a smaller study of 39 patients, which included patients treated before the establishment of the OPRA protocol, two patients reported deep infections. One of them was cured with antibiotics, and the other had the implant removed. It is worthy of notice that the cause of infection could not be directly related to the percutaneous interface, and overall, it was found that infections rarely lead to disability or implant removal (Tillander *et al.*, 2010).

In relation to the skin interface, the OPRA treatment indicates that 1) soft tissue at the stump must be stabilized in order to reduce skin displacement during motion, and 2) subcutaneous fat must be removed in order for the skin to attach to the underlying bone structure. These principles have been independently suggested as fundamental for a successful percutaneous interface (Affeld *et al.*, 2012). Furthermore, relative motion has been suggested as the main catalyst of infections in previous percutaneous interfaces (Pitkin, 2013).

The interface between the skin and nails is a successful evolutionary solution that follows the aforementioned principles. Other approaches, such as growing skin into porous percutaneous components have paradoxical complications due to the keratinocytes (predominate cells in the epidermis) actually growing into the device (as designed), which prevents them from sliding and migrating to the top layer at the end of their life cycle, thus causing a sulcus (depression) around the device where bacteria can thrive (Affeld *et al.*, 2012).

Topographic modifications to the implant surface have long been explored as means of reduction of bacterial adhesion and prevention of biofilm creation, however, with conflicting results (Shah *et al.*, 2013). Nevertheless, these continue to be explored together with surface modifications that promote osseointegration (Brånemark *et al.*, 2011), which has been incorporated to the new generation of fixtures in the OPRA Implant System, after being clinically successful in dental implants (Thomsson and Larsson Wexell, 2013).

Additional suggestions have been given to improve the skin interface. One of them is broadening the bone area around the implant, which effect has been calculated to reduced shear stress (Yerneni *et al.*, 2012). This or other methods to further improve the skin interface, such as antibacterial coatings (Zaborowska *et al.*, 2014), are currently explored by our group and others.

Clinical Outcomes

OPRA has shown to increase prosthetic use and mobility when compared with socket suspension (Hagberg *et al.*, 2008). In transfemoral amputees, it has shown to provide a wider hip range motion (Hagberg *et al.*, 2005; Tranberg *et al.*, 2011), and reduced pelvic tilt (Tranberg *et al.*, 2011). However, despite of osseointegrated patients showing a more normal gait pattern over socket users, these were not equal to those from able-bodies (Frossard *et al.*, 2010). This is potentially because prosthetic attachment alone does not automatically provide full control over the prosthesis, as able-bodies have over their extremities, and also because transfemoral amputees lack of powered knee and ankle joints.

Osseointegrated patients have reported a reduced perception of disability and energy consumption (Sullivan *et al.*, 2003; Lundberg *et al.*, 2011). Moreover, osseointegrated prosthesis have been described as a more integral part of the patient, rather than viewed as an external tool (Lundberg *et al.*, 2011). The latter might in part be due to a phenomena called *osseoperception*, which describes the patient's ability to better perceive the environment due to the direct transmission of load and vibration from the prosthetic limb to the bone (Brånemark *et al.*, 2001). An improved sensory feedback from the surroundings has been anecdotally reported by osseointegrated patients regardless of the level of amputation. This led to scientific investigations in which OPRA patients showed a higher perception of vibratory and pressure stimuli over socket users (Jacobs *et al.*, 2000), as well as themselves before osseointegration (Häggström *et al.*, 2013b). Moreover, it has been found that tactile stimulation in osseointegrated finger prostheses activates the corresponding somatosensory areas in the brain, which was investigated after reports of patients being able to identify textures and surfaces by touch (Figure 9). The brain activation was found bilaterally, rather than strongly in the contralateral side to the amputation, which was suggested as a compensatory mechanism (also observed in other conditions such as stroke) due to the missing biological sensors in the amputated hand (Lundborg *et al.*, 2006). This finding supports the notion that along with the mechanosensibility associated with osseointegrated implants, osseoperception also results in brain plasticity maintaining sensory function (Klineberg *et al.*, 2005).

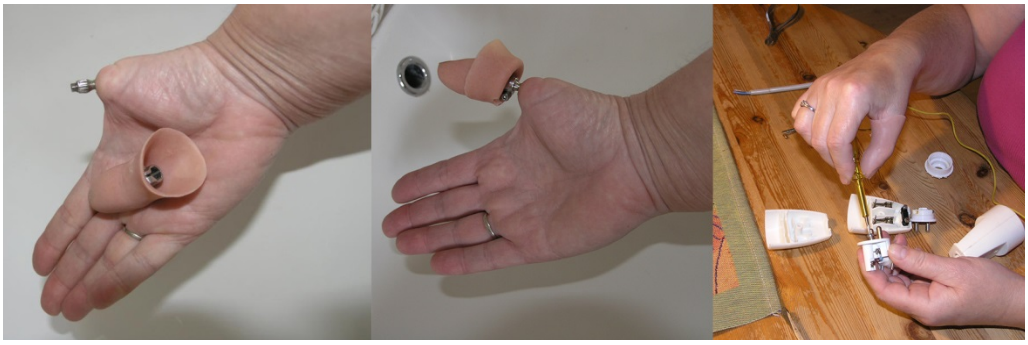

Figure 9. The osseointegrated thumb prostheses allow full range of motion in the adjacent joint and a high degree of sensory feedback, thus restoring functionality (right inset).

Overall, the OPRA treatment has shown to improve the patients quality of life (Sullivan *et al.*, 2003; Hagberg *et al.*, 2008; Brånemark *et al.*, 2014). Patients have described it as a revolutionary change, adding existential implications to the quality of life, where they can "*be more engaged in their life and social interactions rather than focusing on a scrambling socket chafing their skin or aching and pinching*", thus the impact of osseointegrated prosthesis has been observed beyond functional improvements. Patient can participate in activities from which they were restricted due to the socket suspension, such as dancing or cycling (Figure 10-11), and since they are now less limited, they can get more involved in self-development (Lundberg *et al.*, 2011).

Figure 10. Transfemoral osseointegrated patient who is a certified body-pump instructor and cycled approximately 320 km from London to Paris using her osseointegrated prosthesis[5].

Figure 11. Transhumeral and transfemoral osseointegrated patient who is a Paralympic swimmer[6].

[5] Central image by FitPro (www.fitpro.com) with permission.

Our research group and others have observed that once the limitations of the socket coupling has been overcome, patients have higher expectations now limited by the artificial limb and its control (Sullivan *et al.*, 2003). The latter being the main focus of this thesis.

Economic Matters

Patients treated with the OPRA Implant System have shown an approximately 50% reduction on the number of visit to the prosthetic workshop (Häggström *et al.*, 2013a). This can be explained by considering that sockets require to be exchanged in average every 2 years (Dillingham *et al.*, 2001). Socket related issues have been found as the main cause for visiting the prosthetists workshop over problems relating the prosthesis itself or cosmetic covers (Häggström *et al.*, 2013a).

Despite that prosthetic coupling and safety components utilized in bone-anchored prosthesis differ from those utilized with sockets (Jönsson *et al.*, 2011), a recent retrospective cost analysis found that prosthetists spend considerably less time (∼50%) fitting and maintaining limb prosthesis in osseointegrated patients. Furthermore, despite that OPRA patients use more sophisticated prosthetic devices, the overall cost was found similar since they require fewer visits and personnel working hours (Häggström *et al.*, 2013a). This study did not include implant and surgical costs.

As expected, a treatment requiring a surgical intervention including an implant has a higher immediate cost over conventional socket suspension. However, the long-term costs must not be overlooked. In the case of the Hospital del Trabajador in Santiago de Chile, Chile, 23 of 25 patients successfully treated with the OPRA Implant System are able to continue their professional activities[7]. One could argue that the cost related to a life-long disability can be higher than an initially more expensive treatment if such treatment reduces the disability, and thus reduces related costs over time.

[6] Pictures by Karin Nauclér.

[7] Personal communication April 2014 - Dr. Rainhold Garcia, published with permission.

Human-Machine Communication

Percutaneous Leads

Percutaneous leads have been employed widely in experimental research in functional electrical stimulation. A retrospective study on intramuscular electrodes with percutaneous leads (62 subjects) found that 14.5% of patients reported at least one infection event in the skin interface (Knutson *et al.*, 2002). The longest time these leads were implanted was approximately one year, and therefore it is unknown how infections and other mechanical instabilities will affect the implant survival in longer periods of time. It has been widely suggested that percutaneous leads will eventually lead to infections, which would ultimately result in the device failure (Stein *et al.*, 1980; Hoffer and Loeb, 1980; Dhillon *et al.*, 2004), arguably due to poor immobilization of the lead at the percutaneous site (Affeld *et al.*, 2012). Thus reliability, safety, and cosmetics problems are associated to percutaneous leads (Weber *et al.*, 2012).

Percutaneous leads require external connectors that must be stabilized on the skin (Figure 12), *e.g.*, using an adhesive tape. This raises several practical questions such as: How easy would it be for the patient to wear the prosthesis and make electrical coupling with a skin-fixed connector? How long can the skin-obstructive bandages and tapes remain in place? Are there skin related problem due to the adhesive tapes? How comfortable it is to have adhesive tapes over the skin for long periods of time? One protocol has been prescribing removal of the bandages and clean the site with alcohol once or twice per week (Knutson *et al.*, 2002), which might be painful due to the open skin.

Additionally, a catastrophic failure would be the result of accidentally pulling the connector and leads in activities of the daily living, *e.g.*, undressing, making sports, playing with children, etc. Therefore it is also important to consider the disabling consequences imposed by such system, *i.e.*, are the subjects free to swim and shower without putting their device at risk?

Despite not being regarded as a long-term stable solution, percutaneous leads play an important role in research and clinical practice, such as the preliminary evaluation of a neurostimulation based therapy before proceeding with a permanent implantation.

Figure 12. Percutaneous leads with skin surface connector. Left inset - electrode leads exiting from skin surface (A), connector block (B), and stimulator cable (C). Right inset- bandage (D) covering implant site and connector block-stimulation cable interface. Illustration from the open access article: Knutson *et al.* (2002).

Wireless systems

In this time of electronic mobility, wireless technology is an obvious solution for the challenge of communicating the implanted electrodes and the artificial limb. In paper I, advantages and disadvantages of wireless technologies for recording and stimulation are briefly discussed, and special attention was given to the Implantable Myoelectric Sensors (IMES [Weir *et al.*, 2009]). As opposed to distributed systems where each implant has telemetry capabilities, such as the IMES and previous work by Herberts *et al.*, (1968), centralized systems where electrodes are connected via leads to a single transmission and control unit have also been developed specifically aimed for the control of prosthetic limbs (McDonnall *et al.*, 2012; Lewis *et al.*, 2013), as well as for more convenient physiological studies (Axelsson *et al.*, 2007). These systems have had unidirectional focus solely on recordings, however, there are reports of bidirectional neuroprostheses employing similar wireless technology (Hart *et al.*, 2011). Wireless systems aimed for prosthetic control have been tested *in-vitro* and *in-vivo* in animal models, and although the general idea was explored in human patients since the 1960's (Herberts *et al.*, 1968; Clippinger *et al.*, 1974, 1981), it is not until now that a clinical implementation is pursued again (Pasquina *et al.*, under review). Promising results have been recently announced on the implantation of the IMES (Figure 13) in a transradial patient (Hankin *et al.*, 2014), as part of a clinical trial filed in May 2013[8]. Currently, this system requires a series of external components to operate, which most likely will be miniaturized in order to be embedded on the prosthetic arm.

[8] Study registered at ClinicalTrials.gov, ID: NCT01901081, "Feasibility of Implantable Myoelectric Sensors to Control Upper Limb Prostheses (IMES)" (accessed: Apr, 2014).

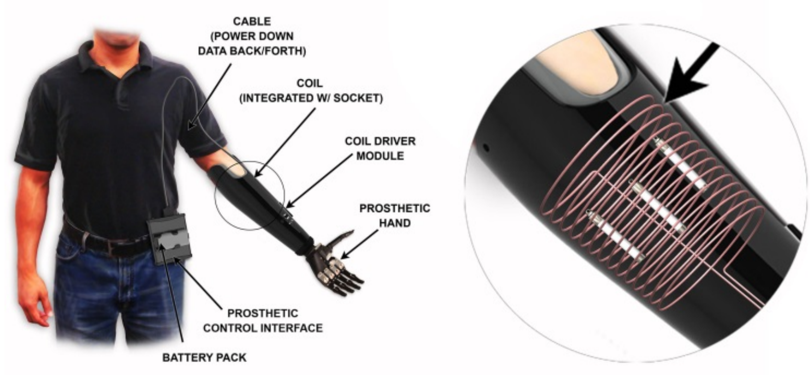

Figure 13. The Implantable Myoelectric Sensors (IMES) originally developed by Weir *et al.* (2009), and currently in the process to reach clinical implementation by the Alfred Mann Foundation, USA (Merrill *et al.*, 2011; Pasquina *et al.*, [under review]). Illustration by the Alfred Mann Foundation used with permission.

Wireless systems for neural recordings in the central nervous system are also showing promising results (Sharma *et al.*, 2011; Borton *et al.*, 2013a). Borton *et al.* have recently reported on a fully implantable device capable of transmitting neural data from a microelectrode array at considerably fast speed (24 Mbps). This device can operate continuously during 7 hours before requiring to be recharged via induction (Borton *et al.*, 2013a). Similarly to the approaches on the peripheral nerves, clinical implementation has not been reported. On the other hand, fully implanted and wireless neurostimulators to treat conditions such as chronic pain or footdrop have been used in human patients since early 1970's (Nashold *et al.*, 1982; Waters *et al.*, 1975). The contrasting difference might be due to the amount information required to be transferred via the wireless link. Pacemakers and neurostimulators commonly use the wireless link solely to transfer programing parameters, status reports, and on/off signals. A neurally controlled prosthetic limb would require continuous transfer of information which raises the requirements on power consumption and safety. Heating at the antenna site due to constant transmission must be kept below 2°C from the body temperature[9] in order to avoid thermal injury. Identified issues with telemetry systems are power consumption (Axelsson *et al.*, 2007), overheating (Borton *et al.*, 2013a), coupling and orientation (Baker *et al.*, 2010), and susceptibility to electromagnetic interference, as more and more consumer products are enabled with wireless transmission.

It is worth mentioning that even when solving all technical and safety challenges related to wireless systems, these will always have a more limited bandwidth in comparison to a wired solution, as suggested in Paper V. Wireless systems also require superficial

[9] According to the international standard ISO14708-3:2008, Implants for surgery - Active Implantable Medical Devices

components, which can cause a variety of problems ranging from discomfort to disability, particularly if a socket is required. Additionally, the inherent complexity of wireless communication makes it more prone to failures, as we have learned from industrial automation where wireless systems are carefully used owing to the related cost of stopping production due to communication problems. On the other hand, a wireless system leaves the skin intact, and therefore such a solution will always have a place as an alternative to a percutaneous implant, or for patients with shoulder disarticulations where percutaneous osseointegrated implants has not yet been employed.

The Osseointegrated Human-Machine Gateway

As opposed to mechanically unstable percutaneous leads, the idea of employing an osseointegrated device to allow electrical communication between implanted electrodes and limb prostheses is as old as the use of osseointegration in bone-anchored prosthesis (Brånemark, 1993). This rather "straightforward" idea has continued to be suggested in the literature (Dhillon *et al.*, 2004), presented in scientific conferences (Ortiz-Catalan, 2010), and explored in bench and animal models (Ortiz Catalan, 2010; Pitkin *et al.*, 2012; Al-Ajam *et al.*, 2013). The real challenge, however, remained in developing an implant system that preserves the mechanical integrity required for load transfer between bone and prosthesis, and at the same time, allows for electrical communication in and out of the body (bidirectional). The work done during this doctoral thesis is the first to bring this idea to clinical reality (Paper V).

Extensive work previously conducted in neuroprosthetics taught us that epimysial and cuff electrodes are safe, reliable, and well characterized neuromuscular interfaces (Paper I). Moreover, it provided us with enough information to avoid unnecessary animal experiments to validate the feasibility of permanently implantable electrodes as source for prosthetic control. The epimysial electrodes have been extensively used in humans for recording and stimulation as part of neuroprostheses (Kilgore *et al.*, 2005). These have remained implanted for over 20 years and used in activities of the daily living (Kilgore *et al.*, 2008). The clinical trial of the FreeHand system reported 408 electrodes implanted in 51 patients, from which only 3 presented failures, and presumably only one due to mechanical fatigue (Peckham *et al.*, 2001). In a related study, 2 out of 204 epimysial electrodes (27 patients) failed with an average follow up of 7.1 years (3.2 to 16.4 years) (Kilgore *et al.*, 2003). In both studies the electrode leads (lengths of 28 to 83 cm in the latter study) crossed up to 3 joints, which increased the mechanical stress to which they are exposed, and nevertheless, high survival rates were observed. Similarly, cuff electrodes have been extensively used in humans to treat chronic pain (Nashold *et al.*, 1982), tinnitus (Ridder *et al.*, 2013), epilepsy (Tahry *et al.*, 2010; Ben-Menachem *et al.*, 2013), sleep apnea (Schwartz *et al.*, 2001), and blindness (Veraart *et al.*, 1998; Delbeke, 2011), as well as for restoring upper (Haugland and Sinkjaer, 1995; Polasek *et al.*, 2009; Memberg *et al.*, 2014) and lower (Waters *et al.*, 1985; Haugland and Sinkjaer, 1995) limb function in patients with tetraplegia or hemiplegia, respectively.

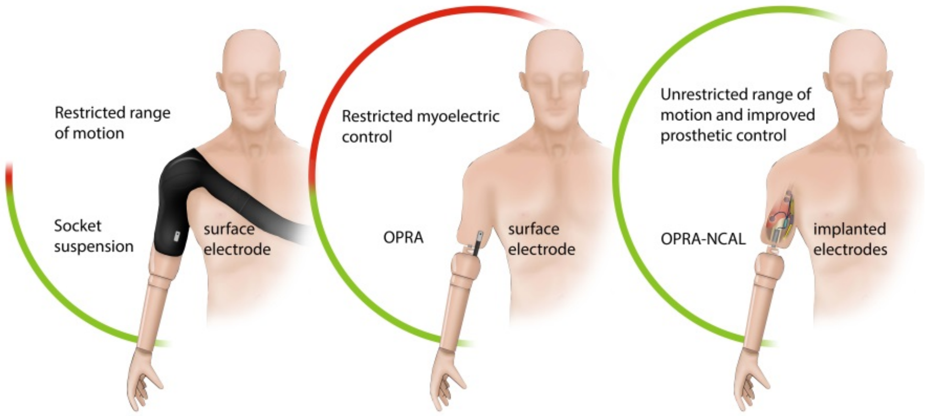

Figure 14. The left inset shows a common socket fitting for a high transhumeral amputee limiting the range of motion (green line) and prosthetic control at certain height (red line). The OPRA treatment releases the adjacent joint and allows for full range of motion (central inset). However, the controllability of the prosthesis is compromised in certain limb position due to myoelectric cross-talk from adjacent muscles (red line). The enhancement of the OPRA treatment to provide a more natural control of artificial limbs (NCAL) allows for permanently implantation of neuromuscular electrodes to robustly provide long-term stable signals for control, independently of limb position or environmental conditions.

As previously mentioned, bone-anchored prostheses allow for full range of motion of the remaining joints. However, myoelectric control can be compromised in certain limb position when utilizing surface electrodes due to myoelectric interference from adjacent muscles (Figure 14). This was a major problem for the first recipient of the OHMG, as the restricted myoelectric control was particularly disabling in professional activities. Moreover, the control was considerably affected in outdoor activities during the winter time due to poor conduction at the skin interface (a recurrent problem living in the north of Sweden). By employing implanted neuromuscular electrodes, the skin interference is eliminated from the recording path, together with the skin related issues. As a result, the controllability of the prosthesis becomes independent from limb position and environmental conditions (Paper V). Moreover, since the electrode is closer to the source, the control signals no longer require traveling through soft tissue, skin, and potentially dead skin cells before reaching the electrode, which translates into lower muscular effort and increased grip resolution and proportional control (Paper V), as expected from an increased signal bandwidth.

The OHMG was designed modularly in order to keep within the philosophy of the OPRA implant system (Figure 7). More importantly, the percutaneous and osseointegrated components (abutment and fixture, respectively) were kept intact to secure the mechanical stability required for load transfer between the prosthesis and the bone, as well as reduced disturbances at the skin interface. The abutment screw was modified to embed two feedthrough connectors, one *parallel* at the distal end, and one *in-line* at the proximal end. An *in-line* pin extends from the central sealing component to interface with the proximal connector at the abutment screw, from which signals are transferred via the feedthrough sealing component to leads that extend intramedullary to a connector unit located in soft tissue. The neuromuscular interfaces can be then connected to this latter connector unit in the soft tissue. This modular design allows upgrading or replacing any component with minimum disturbance to the others (Figure 15).

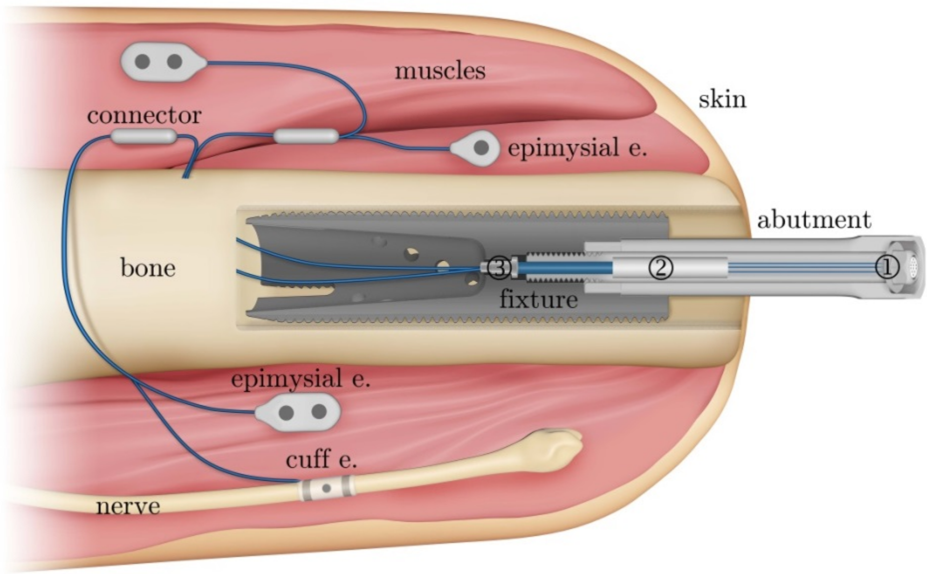

Figure 15. Illustration of the osseointegrated human-machine gateway (OHMG). Loads are transferred from the artificial limb to the abutment, the abutment to the fixture, and the fixture to the bone. The abutment screw (AS), which goes through the abutment to the fixture, is designed to keep the abutment in place. A *parallel* connector is embedded in the AS's distal end (1) to electrically interface the artificial limb. This feedthrough is electrically connected to an *in-line* connector embedded in the AS's proximal end (2). The *in-line* connector interfaces with the corresponding *in-line* pin extending from the central sealing component (3), from which leads extend intramedullary to a connector unit located in the soft tissue. The neuromuscular electrodes are finally mated to this connector.

In this first generation of the OHMG, no active components are implanted but instead the biopotential amplifiers and control electronics are placed in the prosthesis (developed within this thesis). The resulting system is completely self-contained and no components over the skin are required. The patient only needs to couple the prosthetic arm to the abutment (single handed as shown in Video 1 of Paper V), and all electrical connections and functionality is made available automatically. An intermediate connector with concentric rings was developed to allow for the prosthetic arm to be attached in any angular orientation, as spring-loaded contacts will automatically mate with their corresponding pair. This intermediate connector has the purpose to facilitate donning, but more importantly, to protect the abutment screw connector from any accidental torque.

As a novel medical device, the OHMG does not fall within a single regulatory standard. Nevertheless, it was developed within the ISO 13485:2003 standard (Med Dev – Quality Management), and following a variety of international and European standards such as the 93/42/EEC (Med Dev), 90/385/EEC (Active Imp Med Dev), ISO 14708-1 (Active Imp Med Dev), ISO 14708-3 (Active Imp Med Dev, Neurostimulators), and IEC 60601-1 (Med Elect Equip), from which relevant sections were considered.

Biopotential Electrodes

Electric potentials produced by biological systems can be recorded with a variety of electrodes. Dry surface electrodes are used in myoelectric prostheses due to the difficulties in sustaining a stable wet interface on the skin (although applying water is a common practice by patients). Despite that similar recordings have been observed when comparing dry and wet surface electrodes (Chan and Lemaire, 2010; Laferriere *et al.*, 2011), as well as similar MPR performance (Li *et al.*, 2011), the former are more susceptible to noise and motion artifacts. Dry electrodes are normally made of stainless steel or noble metals, which results in a polarized interface (Merletti *et al.*, 2009). The high impedance of such interface (kΩ to MΩ), and its capacitive nature, easily allows for motion artifacts that saturates the amplification electronics. Skin abrasion is recommended when using surface electrodes as this will remove dead skin cells and thus reduce the interface impedance and noise. However, this practice is rarely followed in myoelectric prostheses, arguably because it is impractical for patients. This illustrates the importance of practical solutions if these are to be successful in clinical use. Practical problems around surface electrodes are further described in Paper I along with relevant findings for prosthetic control.

In 2012, a brain-machine interface (BMI) allowed a tetraplegic patient to control a robotic arm within a controlled environment (Collinger *et al.*, 2012). For patients in such conditions, a centralized approach (BMIs) is deemed necessary (for a review in BMIs see Bensmaia and Miller [2014]). In the case of amputees, acquisition of control signals and neurostimulation for sensory feedback can also be done at the spinal cord and peripheral nerves, where filtering of unwanted motor intention and sensory pathways occurs naturally. Because of this reason, electrodes at the peripheral nervous system (PNS), and remnant musculature at the stump, were of the main interest of this thesis (Figure 16).

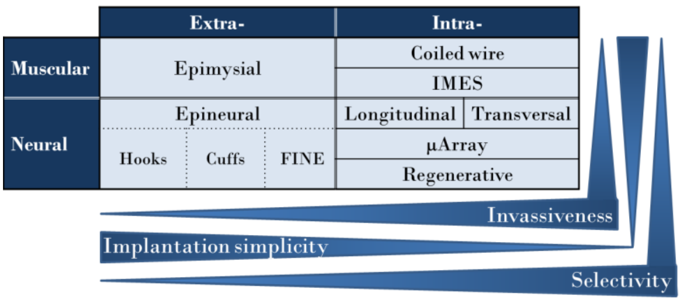

Figure 16. Tradeoffs for different muscular and neural electrodes (Paper I).

A comprehensive review on electrode materials is given by Geddes and Roeder (2003); surface electrodes by Merletti *et al.* (2009); and implantable electrodes by Schultz and Kuiken (2011), in the PNS by Navarro *et al.* (2005), in the CNS by Cheung (2007), and with particular focus on sensory feedback by Weber *et al.* (2012). A review on implantable electrodes with focus on their clinical application to prosthetic control is given in Paper I.

Non-electric interfaces

Neuromuscular activity can be detected in a variety of ways that do not necessarily require an electric coupling, although this is the most commonly used approach. A superconducting quantum interference device (SQUID) can be used to detect the weak magnetic field generated by the flow of ions (Hoshiyama *et al.*, 1999). A major limitation for the clinical use of such device is the considerable cooling and shielding infrastructure required. Other approaches such as acoustic myography, vibromyography, and phonomyography (all together mechanomyography) use microphones or accelerometers to detect muscular activity (Islam *et al.*, 2012). These sensors are accessible and less dependent on the skin interface. In a similar way, ultrasound can be used to measure the variation on muscle thickness resulting from a contraction, defined as sonomyography (Guo *et al.*, 2013). On the invasive side, optogenics is currently the technology that can potentially deliver the highest selectivity for recordings and stimulation (Boyden *et al.*, 2005). All these technologies have advantages and disadvantages in comparison with electromyography or neuromyography, and ultimately, their utility will be demonstrated by their clinical acceptance.

Bioelectric signal acquisition

The differential measurement is the most common method to record bioelectric potentials due to their small amplitude within a noisy environment. Myo- and neuro-electric signals are normally a few mV and μV, respectively, and therefore their amplification is susceptible to intrinsic and extrinsic noise from a variety of sources. Different capacitances can develop between the body and ground; body and power lines; and, leads and amplifiers, which induce interference currents that affect the amplification electronics. Differences in the electrode impedances can cause the common-mode voltage to become differential, thus creating an offset at the amplifier output. Different techniques to avoid these problems and improve bioelectric signal acquisition are given in (Metting Van Rijn *et al.*, 1990). For example, filtering at 20 Hz as the high-pass cutoff frequency and a slope of 12 dB/oct has been recommended to eliminate motion artifacts in surface recordings (De Luca *et al.*, 2010), while 400-450 Hz for the low-pass cutoff frequency is suggested as enough to capture the relevant spectrum of myoelectric activity (Merletti *et al.*, 2009). Additionally, a notch filter to reject the power line frequency is advisable.

The front-end for bioelectric signal acquisition has to carefully consider factors such as the input impedance (rule of thumb, at least 100 times higher than the highest expected electrode impedance [Merletti *et al.*, 2009]), input referred noise (voltage and current), common mode rejection ratio (CMRR), power supply rejection ratio (PSRR), output voltage offset and drift, and leakage current. All the bioelectric amplifiers used in this doctoral thesis were designed by the author using commercially available instrumentation amplifiers as the analog front-end, and following the aforementioned considerations. An advantage of utilizing instrumentation amplifiers in a single integrated circuit (IC) is that passive components are closely matched to reduce undesirable effects due to impedance variations and parasite capacitances. Additionally, a single IC reduces board space, power consumption, and very frequently costs (as these are mass produced). Furthermore, variations in temperature are distributed more homogenously, thus reducing its effect on the amplifier performance. Special attention was made to meet regulatory requirements on safety, particularly to the leakage current, which was kept below 0.1 nA. This is far below the upper limits of 1 μA and 0.1 μA that are required by the ISO14708-1:2000 and EN45502-1 (Active Implantable Medical Devices) standards, respectively.

Bioelectric signal processing

Pre-processing

Noise and unwanted information can be reduced, or ideally eliminated, by frequency and spatial filters as we have a prior knowledge on the characteristics of the desired bioelectric signals. Common cutoff frequencies for EMG were given in the previous section. Frequency filters are normally implemented by hardware to avoid saturation of the following amplification chain, although they can also be programmed in software at the cost of a normally higher delay. In a similar way, spatial filters can be implemented by hardware or software to improve the selectivity of the recorded electric field. The later (Huang *et al.*, 2009), and a combination of both (Huang *et al.*, 2013), have shown to improve MPR. In the case where these filters are not enough, there are other more sophisticated processing techniques such as independent component analysis (ICA) and whitening (Liu *et al.*, 2013). Similarly to the work done with filters, these processing algorithms have shown to marginally improve MPR. Nevertheless, none of them have been tested in real-time, where a higher improvement might still be obtained.

Signal processing and pattern recognition algorithms are commonly run continuously in order to predict motion intent. This continuous approach requires unnecessary computations when the patient is at rest (no motor intention). The author has employed a floor noise detection strategy to prevent unnecessary classifications when no myoelectric activity is sensed, which at the same time prevents misclassifications of low intensity EMG patterns (Paper IV, V). Alternatively, there are other more elaborated methods to detect EMG onset such as using 1-D local binary patterns (McCool and Chatlani, 2012).

Additionally, an optimal selection of the available information sources has evident practical advantages such as reduction of the number of electrodes, acquisition hardware, and computational cost. Methods that facilitate such selection can also facilitate prosthetic fittings by helping to better localize optimal electrode placement. These methods can be as straightforward as an *exhaustive search* or *symmetrical reduction* (Hargrove *et al.*, 2007). In a study using the Kullback-Leibler measure, the authors proposed a quasi-optimal method for channel selection based on probability neural networks (Shibanoki *et al.*, 2013). However, it is worthy of mentioning that none of the previous approaches have been tested in real-time or in a stand-alone implementation, where motion artifacts and electromagnetic interference might affect the classification accuracy.

When employing an array of electrodes over the same muscle, the “optimal” electrode selection can be made based on the electrode recording the highest signal amplitude, and it prevalence as the highest on repeated contractions (Kendell *et al.*, 2012). In the case of myoelectric pattern recognition, where one would like to predict more than one movement from the same muscle or group of muscles, one could select the electrodes within the array with the highest signal amplitude per movement (Figure 17), as was done in Paper V.

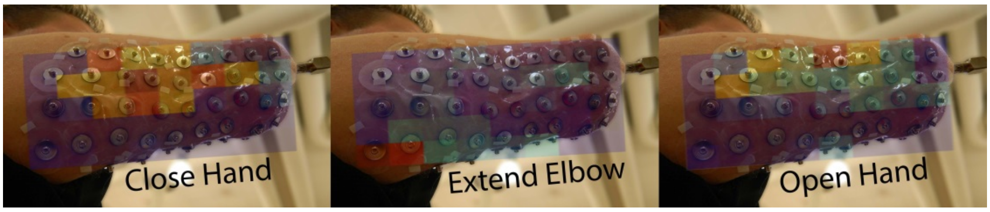

Figure 17. High density surface electromyography (HD-sEMG) used for the selection of electrode placement based on the strongest signals given for predefined movements. A superimposed temperature map shows the electrodes with higher myoelectric activity towards the red color (normalized).

Feature extraction

The neural drive can be extracted in real-time by high-density surface electromyography (sEMG), thus providing considerable information on the number of motor units, and their frequency of activation (Farina and Negro, 2012). Pattern recognition in the form of *decomposition* methods (such as *template matching)* can identify individual motor units with particular action potential profiles. This is particularly useful for the study of the neuromuscular system, to identify neuropathies, and monitoring neuromuscular rehabilitation. However, this is not the level of detailed information traditionally used for the prediction of motor intention when using sEMG, or more recently epimysial EMG (Paper V). Rather than decoding the detailed neural drive, features that characterize the summation of several motor units are more commonly used as the bioelectric signature of different motions.

Trains of individual motor units can be observed when using highly selective electrodes (e.g. intramuscular or intrafascicular), and therefore algorithms that exploit such information are preferred (Micera *et al.*, 2010). As a downside, motor unit decomposition or spikes counting becomes increasingly difficult at higher contraction forces due to cross-talk interference. The majority of the literature report less invasive and single differential sEMG, which delivers a superposition of several motor unit action potentials, and therefore it has been more practical to use amplitude-based or statistical descriptors such as the *mean absolute value* or the *standard deviation*, respectively.

A finite length of the signal must be defined in order to extract such descriptive features. This is commonly refereed as "*time windowing*" or "*signal windowing*", thus the particular name of "*time window*" is given to the snapshot in time from which the *signal features* are calculated. Finally, a feature vector can describe a single or mixed class, for individual or simultaneous movements, respectively. Further details on signal windowing and features are given in Paper III.

Feature selection

As stated by Guyon and Elisseeff (2003), the purpose of feature selection is three-fold:

- Increasing classification accuracy (specific and less redundant descriptors)
- Faster and thus more cost-effective classifiers (reduced training, testing and prediction times)
- Providing better understanding of the underlying processes responsible for the observable data

In machine learning, and specifically pattern recognition, it is not unusual that a given classification problem has a feature space prohibitive for real-time computations (thousands or millions features). The selection of optimal features sub-sets is not only desirable but necessary in such cases. In MPR, the feature space is normally lower than hundreds, thus real-time prediction is still possible, but not necessarily optimal and sufficiently accurate. In Paper III (Table 1), a non-exhaustive list of features and feature sets is presented. Currently, no study has explored all those features together in order to find optimal sets. This is important because how the pattern is represented (features) might have a higher impact on MPR than the classifier itself (Parker and Scott, 1986; Hargrove *et al.*, 2007). Explorative work has been done by the author on the optimal selection of 21 time and frequency features via a genetic algorithm (Ortiz-Catalan *et al.*, 2012).

Features can also be transformed to provide an alternative representation, which can render better separation and reduced redundancy. Algorithms to this end have also shown to improve MPR, such as: Principal Component Analysis (PCA) (Englehart *et al.*, 1999; Kanitz *et al.*, 2011; Liu and Zhou, 2013; Al-Timemy *et al.*, 2013); Individual Principal Component Analysis (iPCA) (Camacho *et al.*, 2013); Orthogonal Fuzzy Neighborhood Discriminant Analysis (OFNDA) (Al-Timemy *et al.*, 2013); and Common Spatio-Spectral Pattern (CSSP) (Huang *et al.*, 2013).

Currently, no feature selection or transformation algorithm seems to be necessary for an accurate prediction of motor intention. This is because pattern recognition algorithms alone already produce a considerably higher accuracy, but again, real-time testing might show otherwise.

Myoelectric Pattern Recognition (MPR)

As can it be deduced from the previous section on feature extraction, the use of the term *myoelectric pattern recognition* (MPR) in the context of this thesis is aimed to the prediction of motor intention, rather than the identification of motor unit action potentials.

Information from individual motor units might as well be used for the prediction of motor intention. However, this requires the use of high-density sEMG (HD-sEMG) electronics that although becoming more portable (Barone and Merletti, 2013), recording from dozens of electrodes simultaneously while keeping a good skin contact over long-periods of time makes this approach more cumbersome than using fewer electrodes. Four to six bipolar electrodes, which already causes several stability issues, have been shown to be enough in a variety of MPR experiments (Hargrove *et al.*, 2007; Farrell and Weir, 2008; Li *et al.*, 2010), including simultaneous (Young *et al.*, 2013) and finger control (Al-Timemy *et al.*, 2013). Nevertheless, since no conventional MPR system has been successful in clinical use (Farina *et al.*, 2014), MPR based on motor unit decomposition via HD-sEMG might still have something to offer, as well as electrode grids with lower density (Tkach *et al.*, 2014).

A general computational flow chart for advanced prosthetic control strategies based on MPR is shown in Figure 18. This modular design includes signal acquisition, treatment (pre-processing), feature extraction, pattern recognition (including feature selection and classifier topologies), and control (post-processing). All these segments are further described within this thesis and can be practically explored in the open access platform introduced in Paper III (BioPatRec).

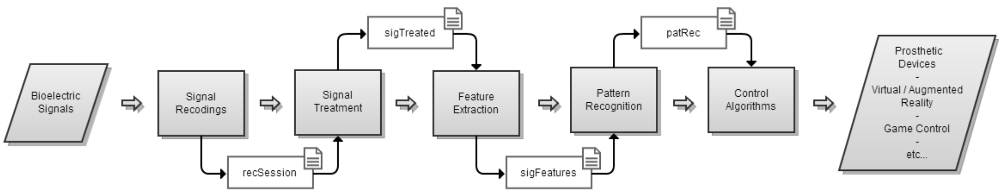

Figure 18. Computational flow chart for advanced prosthetic control strategies based on myoelectric pattern recognition. This particular design is the fundamental framework of BioPatRec, a modular platform for research, development and benchmarking (Paper III).

Pattern Recognition

Pattern recognition is an umbrella term for a variety of algorithms that range from purely statistical (e.g. linear discriminant analysis), to biologically inspired (e.g. artificial neural networks). The terms *classifier, predictor,* and *decoder* are normally used interchangeably to denote an instance of such algorithms. *Pattern recognition algorithms* (PRAs) require input given in data sets (feature vectors) that characterize the *classes* or *labels* (these two terms also used interchangeably), which in this particular field refers to *movements* or *postures (e.g. hand close)*. PRAs might need an iterative training processes (learning) or calibration (less iterative). The latter could also be seen as *learning*, even if there is a predefined baseline; it is all about semantics (not a subject of this thesis). The training or calibration can be supervised (labels known) or unsupervised (labels unknown) (Sensinger *et al.*, 2009). Other mathematical approaches (Jiang *et al.*, 2009; Rasool *et al.*, 2013), which are normally biologically inspired, have been described as *model-based* rather than *pattern recognition*. This is despite that both literary serve the purpose of differentiation of myoelectric patterns to predict motor intention. For that reason, all algorithms used for the differentiation/decoding/classification/prediction of myoelectric signals are considered MPRs within this work.

There has historically been a variety of algorithms used for the prediction of motor intention using myoelectric signals. Discriminate Analysis (DA) methods occupy the first place in the literature as the most commonly used algorithms, in particular Linear Discriminate Analysis (LDA). These statistical approaches have been used as far back as the first implementations of MPR (Herberts *et al.*, 1973, 1978). More recently, LDA has been the preferred algorithm used by two influential research groups (Rehabilitation Institute of Chicago and University of New Brunswick), which might explain its prevalence in the literature. LDA has shown merit for being a relatively simple and fast training/prediction algorithm, but more importantly, with a performance similar to other more "sophisticated" classifiers (Scheme *et al.*, 2011).

Artificial Neural Networks (ANNs) are probably the second most used algorithms in MPR, in particular the Multilayer Perceptron (MLP), but also Self-Organizing Maps (Eriksson *et al.*, 1998), Probabilistic Neural Networks (Shibanoki *et al.*, 2013), Time Delayed Artificial Neural Networks (Pulliam *et al.*, 2011), and Tree-structured Networks (Sebelius *et al.*, 2005) have been used. MLP and LDA have been historically compared, and even combined (Amsuss *et al.*, 2014), with variable results regarding offline accuracy (Englehart *et* *al.*, 1999; Hargrove *et al.*, 2007; Huang and Kuiken, 2009). LDA has been found to outperform MLP in the real-time prediction of individual movements (Paper III), on the other hand, MLP has shown to be more suitable for simultaneous control (Paper IV).

Algorithms used to a lesser extent are Gaussian Mixture Models (Huang *et al.*, 2005), Hidden Markov Models (Chan and Englehart, 2005), and Support Vector Machine (Oskoei and Hu, 2008; Shenoy *et al.*, 2008). Regression techniques, such as linear regression, mixture of linear experts, and kernel ridge regression (Hahne *et al.*, 2014), produce a continues output rather than a binary prediction, which is more attractive for the prediction of kinematics and proportional control (also doable with MLP). Similarly, the Non-negative Matrix Factorization (NMF) algorithm has been argued to be exceptionally useful to predict unseen patterns such as simultaneous movements (Jiang *et al.*, 2009; Ajiboye and Weir, 2009), although not particularly better than MLP when directly compared (Jiang *et al.*, 2009, 2013c). Lastly, a more recent and distinctive approach based on PCA and postural synergies (joint angle transformation), namely Morphing Hand Posture Control, has shown to accurately predict up to 13 joint angles for hand grasping (Segil and Weir, 2014).

The main argument for employing pattern recognition in the context of prosthetic control is that signal separation is considerable hard to achieve by selectively spacing surface electrodes, and thus a direct link between one muscle and one prosthetic action (*direct control*), becomes unreliable for more than a couple of movements. Furthermore, studies in individual (Hargrove *et al.*, 2013a) and simultaneous control of upper (Young *et al.*, 2014) and lower limbs prosthetics (Hargrove *et al.*, 2013b), have found MPR to improve controllability even in cases where direct control is possible, such as in patients that have undergone TMR. Moreover, MPR has been successfully employed to predict motor intention in other patient populations such as incomplete spinal cord injuries (Liu and Zhou, 2013) and stroke (Lee *et al.*, 2011; Geng *et al.*, 2013), as well as for the treatment of phantom limb pain (PLP) in combination with augmented reality and gaming (Ortiz-Catalan *et al.*, 2014). In the latter study and Paper V, the author demonstrated that it is possible to reliably predict movements indirectly related to the muscles from which the myoelectric signals are recorded, as long as these are activated as support (muscle synergies). This has been shown in real-time for hand open/close, wrist pro/supination, and elbow flexion/extension using signals from muscles at the upper arm (Paper V). However, the reliability of this strategy still needs to be tested in activities of daily living, as this has only been demonstrated while the patient was sitting in a static position.

The prediction of motion intent can be done at different levels, from a binary intention (e.g. wrist flexion or not) to more detailed characteristics of the movement (kinematics) such as speed and target angle (e.g. wrist flexion to 45° moving at 2 deg/ms). Speed and strength are currently addressed in conventional myoelectric prosthesis by proportionally relating EMG strength to force or velocity (*proportional control*). MPR-based strategies have also included proportionality, either within the algorithm itself, or with additional average amplitudes scaled to strength or speed. MPR with proportional control of the latter type has been shown to outperform MPR alone (Simon *et al.*, 2011c), while training with dynamic contraction force seems to improve the classifier real-time performance (Scheme and Englehart, 2013a). More recently, a similar method including a threshold-constrained range showed to outperform the original mean averaging and an exponential method in a 1-D real-time test where only 1 DoF was predicted at the time (Scheme *et al.*, 2014).

Most of the research work in MPR has been focused on predicting motion intent alone (binary). However, some groups have explored the direct prediction of joint angles (kinematics). Currently, no considerable differences have been found when the training target is either joint force or angle, as long as the muscular activity is comparable (Ameri *et al.*, 2014). From the classifier's viewpoint, the algorithms themselves do not actually incorporate information on the meaning of the matching output. From the users and operational viewpoint, however, differences might appear due to the intuitiveness of control and relative electrode displacement during the isometric contractions (varying joint angle and thus muscle length).

More importantly, it has been suggested that further refinement of MPR is not necessary (Jiang *et al.*, 2012a), as current methods which optimistically report almost perfect accuracies are not yet available outside the research laboratories (Farina *et al.*, 2014). Moreover, we can observe an apparent plateau of classification performance by a variety of algorithms (Hargrove *et al.*, 2007 and Paper III, IV); an observation not only restricted to prosthetic control, but also to PRAs in general (Ho *et al.*, 2006). Nevertheless, the possibility still remains that more sophisticated signal processing techniques, as well as feature selection and extraction algorithms, might provide the currently lacking robustness to MPR, and thus become a solution reliable enough for clinical implementation.

Simultaneous MPR of mixed movements

It has been suggested that pattern recognition algorithms are not capable of simultaneous prediction of mixed movements (Jiang *et al.*, 2009, 2013a; Roche *et al.*, 2014; Farina *et al.*, 2014), probably due to the ambiguity around the term "pattern recognition" as discussed previously. However, our work and others have shown that a variety of pattern recognition algorithms can successfully accomplish such task (Al-Timemy *et al.*, 2013; Ameri *et al.*, 2014), and without necessarily increasing the number of classes (Ortiz-Catalan *et al.*, 2013a, 2013b and Paper IV). Similarly, proportional control has been pointed out as a limitation of pattern recognition (Roche *et al.*, 2014), but again, this only applies to certain algorithms, *i.e.*, ANNs can be trained to predict proportionality along with simultaneous movements (Muceli and Farina, 2012), as well as a variety of regression algorithms (Hahne *et al.*, 2014). Moreover, there are no "official" delimitations on where algorithms start and end. For instance, an ANN could be trained to recognize simultaneous movements while a parallel one trained to work out proportionality, a new name could be given to such arrangement, and thus a "new" PRA would be created that could do both, proportional and simultaneous control. Moreover, due to the high speed of computation of ANNs, and currently available processing hardware, such algorithm would produce an acceptable real-time response for the application in question (myoelectric control).

In the last decade, a growing interest on providing more intuitive control has led to the exploration of simultaneous control strategies, which were initially studied *offline* (Yatsenko *et al.*, 2007; Jiang *et al.*, 2009; Pulliam *et al.*, 2011; Muceli and Farina, 2012; Jiang *et al.*, 2012b, 2013a), and more recently in *real-time* for 2 DoF (Muceli *et al.*, 2013; Jiang *et al.*, 2013c, 2013b; Young *et al.*, 2014; Ameri *et al.*, 2014; Tkach *et al.*, 2014) and 3 DoF (Ortiz-Catalan *et al.*, 2013a, 2013b and Paper IV). It is worthy of notice that most of this research has been published in the last year, and most likely conducted independently between the different groups. Previously, research on MPR was focused on the prediction of individual movements, although there are early reports of simultaneous MPR in the 1970's and 1980's (Herberts *et al.*, 1973; Saridis and Gootee, 1982). The possibility of simultaneous control was an early request by patients (Atkins *et al.*, 1996), who not surprisingly also have expressed preference for systems that allow this (Young *et al.*, 2014).

While some approaches such as a NMF and ANN can potentially handle increasing DoF, others based on majority voting (*e.g.* LDA) and *label power set* (Tsoumakas and Katakis, 2007), might face increasing difficulties as the number of DoF increases. Nevertheless, all approaches still need to prove their utility in such cases (> 3 DoF).

The author and others have observed that simultaneous MPR normally produced lower accuracies when classifying individual motions in comparison with individual MPR (Young *et al.*, 2014 and Paper IV). In order to improve this situation, the author has proposed a simple solution in which the activation threshold of the output neurons in a MLP can be adjusted by the user in real-time (Ortiz-Catalan *et al.*, 2013b).

Evaluation of MPR strategies

MPR strategies have been mostly evaluated *offline*, which means that the reported accuracy (or coefficient of determination [R^2] for kinematics) of a given classifier is computed with pre-recorded data. A recording session is normally divided in training/validation and testing sets, where the latter is unseen by the classifier until it has been trained, and therefore it is assumed to be a good estimate of classification performance, *i.e.*, if three repetitions of all involved movements were recorded, the corresponding feature sets are randomized, and then data equivalent to one of the repetitions is separated from the training/validation pool, and is only used for testing.

Intriguingly, the offline accuracy has been repeatedly found as a poor indicator of real-time performance (Lock *et al.*, 2005; Li *et al.*, 2010; Scheme *et al.*, 2011). Algorithms with similar offline accuracy can have a wider spread in real-time, but more importantly, algorithms with an apparent poorer offline accuracy can outperform the others in real-time (Paper III). This is in line with reports suggesting that high offline accuracy is not always necessary for an acceptable real-time control (Jiang *et al.*, 2013c). Nevertheless, these findings strongly suggest real-time testing as a necessary evaluation when proposing advanced prosthetic control strategies. One reason for authors refraining from performing real-time evaluations might be due to the lack of acquisition hardware or software routines, particularly a virtual reality environment. This was one of the motivations for the open source release of BioPatRec (Paper III), which provides real-time evaluation routines such as the Motion and Target Achievement Control tests, together with a virtual reality environment. These tests were originally developed at the Rehabilitation Institute of Chicago (Kuiken *et al.*, 2009; Simon *et al.*, 2011b), and implemented with modifications described in Paper III and IV. Such modifications include the increment of the required correct predictions in order to consider a motion completed (20 versus 10 in the original motion test). This was important because in our experimental setting, 10 predictions were easily achieved, potentially due to the classification speed (predictions every 50 ms). A similar situation was observed if the original 2 second dwell time, as used in (Simon *et al.*, 2011b, 2011a; Young *et al.*, 2012 and Paper IV), was reduced to 1 second (Scheme and Englehart, 2013b; Scheme *et al.*, 2013, 2014; Ameri *et al.*, 2014; Kamavuako *et al.*, 2014; Tkach *et al.*, 2014) or less (Jiang *et al.*, 2013c, 2013b; Muceli *et al.*, 2013), as done in the same or other controllability tests. Decreasing the dwell time would potentially increase completion rates (Hochberg *et al.*, 2006). Because all these variables might affect the end results, it is extremely important for the reproducibility that all the relevant information of the experimental setup is reported, but more importantly for the sake of comparison, that it is consistently followed. However, even when the same experimental protocol is followed, different subjects can produce a different outcome. In MPR (Bunderson and Kuiken, 2012; Ortiz-Catalan *et al.*, 2013b, 2014), as well as in BMIs (Collinger *et al.*, 2012), practicing is known to improve the performance over time (subjects learning), thus the experience of the subjects play an important role (Figure 19-20). The ideal situation would be to compare algorithms under the same circumstances and in the same subjects, which would be facilitated by using a common evaluation platform where all algorithms can be implemented directly by the proposers, such as the one suggested in Paper III (BioPatRec).

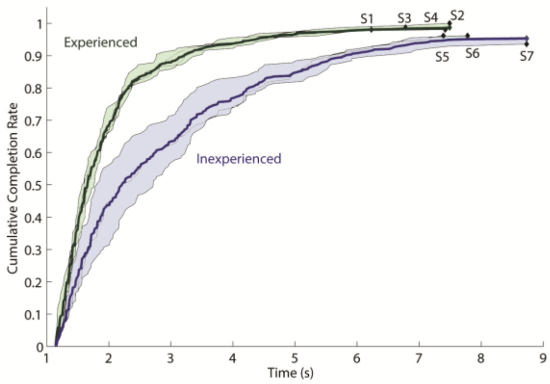

Figure 19. Difference between experienced and inexperienced subjects completing a real-time test of simultaneous control of 3 degrees of freedom. Figure from the article Ortiz-Catalan *et al.* (2013b).

The second best alternative when no real-time evaluation can be performed would be to utilize the same data sets for benchmarking. For some conditions such as neuropathic pain, open data bases for the variable parameters of spinal cord stimulation are available (Meier *et al.*, 2013), however, this has not been the case for MPR. BioPatRec provides a hosting platform for a shared repository of myoelectric signals related to limb movements. Recordings from 20 and 17 subjects have been made available for individual and simultaneous hand and wrist movements (Paper III, IV). These are the largest sets used in any published MPR study known to the author.

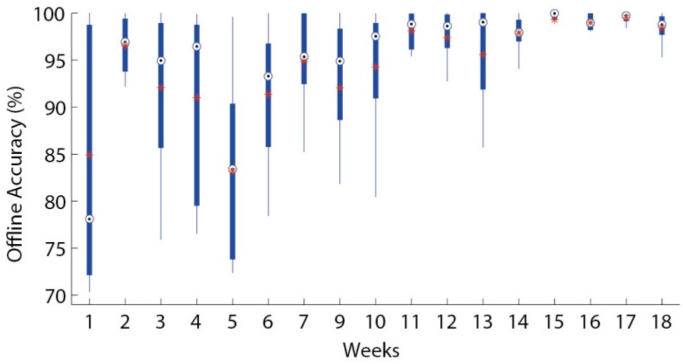

Figure 20. The increment in classification accuracy illustrates the learning progress of a subject that suffered a quasi-elbow-disarticulation 48 years earlier, and trained (once per week) in the execution of 8 movements (hand open/close, wrist flexion/extension, wrist pro/supination, and elbow flexion extension). These movements were decoded by MPR using sEMG at the stump. Figure from Ortiz-Catalan *et al.* (2014).

Evaluations on Able-Bodies versus Amputees

A common disclaimer (or selling point) in the MPR literature is that algorithms or proposed control strategies must be tested in amputees. While there is wide agreement and validity in this argument, it can be argued that not all evaluations require the inclusion of amputee populations, and one must conduct the appropriate tests to support a given claim. For instance, comparisons between different classifiers have shown to hold between able-bodies and amputees (Scheme *et al.*, 2011; Jiang *et al.*, 2013c; Young *et al.*, 2013; Al-Timemy *et al.*, 2013; Liu *et al.*, 2013), i.e., if algorithm *A* outperforms algorithm *B* in able-bodies, algorithm *A* also outperforms algorithm *B* in amputees. If the same musculature is targeted in both groups (which is normally the case, *e.g.*, transradial systems place the electrodes proximally in the forearm where the anatomy is preserved), there is no neuromuscular disorder, and both tests are conducted in the same environments, why would there be differences between algorithms decoding myoelectric signals from comparable anatomy and operating conditions? Admittedly, a different scenario is presented if the musculature is reduced, or there is additional scar-tissue, or basically any anatomical alteration is present in the amputee. This situation would certainly affect the myoelectric patterns as the sources would be affected, however, even in this case it is still likely that algorithm *A* outperforms algorithm *B*, under the rationale that it already does it in an “easier” condition, and the new “more difficult” condition would affect both algorithms.

Reliability of MPR

MPR algorithms have been mostly evaluated in controlled conditions such as at constant temperature and with the subjects being relatively static. However, in real life operation, MPR faces a variety of dynamic conditions that have been shown to be detrimental to its performance.

Electrode shift is expected when using surface electrodes due to skin motion within the socket and due to donning/doffing of the prosthesis. It has been found that targeted placement of the surface electrodes makes the MPR more sensitive to electrode shift, thus equally spacing the electrodes seems advantageous for reliability (Young *et al.*, 2011, 2012). An additional strategy that has shown to improve MPR reliability is to increase the traditional bipolar inter-electrode distance from 2 cm to 4 cm (Young *et al.*, 2012). Moreover, 4 cm inter-electrode distance has shown to increase the EMG information content over 2 cm and 6 cm (Farfán *et al.*, 2010). While placing the bipolar electrodes longitudinally to the muscle fibers is recommended to increase the amplitude of the recorded signal, it has also been found that the addition of few transversal bipolar electrodes can be beneficial for MPR stability (Young *et al.*, 2012).

Variations on limb position (*e.g.* elbow flexed at 0° versus 150°) have also been identified to decrease MPR reliability. This could be attributed to myoelectric cross-talk, and electrode shift due skin movements and muscle length changes. Some of these issues can be partially overcome by training the classifiers in different positions and employing additional sensors such as accelerometers (Fougner *et al.*, 2011; Geng *et al.*, 2012). Unfortunately, in cases such as transhumeral amputations where considerable stronger muscles are close to the surface electrodes, the cross-talk interference can completely mask any other signal and therefore diminish the effectiveness of such approaches. Surface electrodes record muscle cross-talk due the volume conduction effect by the soft tissue in between the electrode and the muscle (Kuiken *et al.*, 2003), and as expected, cross-talk increases with the distance from the electrode to the target source. Additionally, the high impedance of the commonly polarized interface easily produces motion artifacts that can directly cause misclassifications.

In summary, most of these issues are mainly related to the use of surface electrodes (Paper I), which might explain why MPR has not been implemented despite clinical efforts since the 1970's (Herberts *et al.*, 1978; Wirta *et al.*, 1978; Almström *et al.*, 1981).

Post-processing and Control Algorithms

Once the prediction of motor intention has been obtained, this can hardly be used as "raw" control signal to drive a prosthetic device. This is because even occasional misclassifications can considerable affect the controllability if no post-processing is applied. For instance, it has been reported that transitions between the aimed movement and rest, as well as the other way around, have caused frustration on the users due to the resulting misclassifications, also named the *bounce-back effect* (Scheme and Englehart, 2013b).

There are a variety of post-processing algorithms applicable to MPR such as 1) *majority voting* (Englehart and Hudgins, 2003), where a buffer is used to discard predictions in minority; or 2) real-time adjustable output thresholds, as employed to improve the classification of individual (Hargrove *et al.*, 2010) and simultaneous (Ortiz-Catalan *et al.*, 2013b) movements; or 3) *floor-noise rejection* (Ortiz-Catalan *et al.*, 2013b and Paper IV), where the system automatically outputs the *rest* (no motion) class if the myoelectric activity is not higher than a certain threshold calculated using the noise during the recording session at the *rest* state (floor noise), which was found particularly useful to avoid misclassification due to the *bounce-back effect*. The latter method can also be considered as a pre-processing algorithm, as no classification is performed below the floor-noise threshold. It is worth mentioning than these methods are not mutually exclusive.

The rejection of misclassifications can also be done in terms of Bayesian probability by assigning a confidence value to each prediction and comparing them with class-specific thresholds. Such a strategy has been shown to outperform the use of *raw* LDA classification in real-time tests (Scheme *et al.*, 2013). Similarly, *learning* approaches where an additional pattern recognition algorithm (MLP) is trained to evaluate prior predictions, as well as the strength of the muscle contraction, has shown higher reliability over *raw* predictions and the *majority voting* post-processing strategy (Amsuss *et al.*, 2014).

In 2011, a novel approach was presented by Simon *et al.,* in which the maximum velocity at which the limb can be actuated is gradually reached if the classifier continuously predicts the same movement (*velocity ramp*). As opposed to *majority voting* in which the correct action is not reflected until the buffer has been overcome, in the *velocity ramp* the predicted movement will be slowly activated since the first prediction. However, it will be stopped whenever is not predicted any longer, thus avoiding overshooting as commonly done by *majority voting* (Simon *et al.*, 2011a). This approach can be combined with the aforementioned strategies and it is suitable for simultaneous MPR (Paper IV).

Alternative Prosthetic Control Strategies

Prediction of motion intent has been explored beyond pattern recognition of myoelectric signals. *Postural synergies* have been suggested as an alternative method for prosthetic control (Kaliki *et al.*, 2013). The shoulder's posture can be used to infer the position of elbow and wrist joints in the case of transhumeral amputees. This idea has been tested with motion capture systems (magnetic tracking) in controlled environments, and because of the bulky hardware employed, its usability on activities of daily living still needs to be demonstrated. However, even when the hardware could be substituted by more compact sensors such as accelerometers and gyroscopes, an additional shortcoming of this approach is that individual DoF cannot be independently controlled, which includes the actuation of the terminal device (*e.g.* hand open and close). Moreover, actuation of the terminal device cannot be intuitively achieved, but instead, it is linked to a specific shoulder motion (*e.g.* sternoclavicular protraction), or tied to myoelectric signals in a hybrid approach. Additional alternatives to myoelectric signals are force-sensing resistors, foot pedals, air bladders, and conventional switches. Combinations of these technologies have been used as non-invasive solutions for the control of several DoF (Resnik *et al.*, 2011), with the disadvantage of requiring a high cognitive effort.

Alternative control strategies as the presented above are neither natural nor intuitive, yet if practical for patients, they might restore a higher level of functionality over more "physiologically appropriate" approaches.

Intuitive control by preserving proprioception has been proposed for the control of wrist rotation via an osseo-magnetic link. In this approach, a magnet would be implanted in the residual bone and an external sensor would be used to track its motion to drive the rotator. The feasibility of this approach has been demonstrated in a bench test (Rouse *et al.*, 2011).

Sensory Feedback

Humans rely on a variety of exteroceptive (external) and proprioceptive (internal) sensory information when interacting with the environment, particularly for motor control. It has been shown that learning a repetitive motor task can lead to its successful completion without the need of sensory feedback, however, once uncertainty is introduced (or the first time a task is performed) this can hardly be achieved without it (Saunders and Vijayakumar, 2011). Moreover, additionally to the biological sensors that provide a physical description of the environment, humans and other mammals have dedicated sensory nerve fibers such as the *C-tactile*, which are believed to play an important role in social interaction (Olausson *et al.*, 2010; Ackerley *et al.*, 2014). The loss of an extremity impairs the perception of all this information, and despite the well-known importance of sensory feedback, no commercially available prosthesis today purposely provides sensory information back to the user (Antfolk *et al.*, 2013).

Users of myoelectric prostheses rely on visual and auditory clues to determine the correctness of the interaction of their artificial limb with the environment. This normally requires considerable attention (cognitive effort), thus limiting the activities and the speed of execution that otherwise could be possible. The reduction of such cognitive burden has been reported as priority by power prosthetic users (Atkins *et al.*, 1996), as sensory feedback ranks as one of the lowest aspects in users satisfaction (Kyberd *et al.*, 2007).

Commercial prosthetic devices currently embed sensors for their internal control (self-regulation). These allow features such as adaptive grip and slip detection[10]. In the research arena, external sensors have been developed for prosthetic applications which are capable of providing tactile information beyond that of human finger tips (Fishel and Loeb, 2012). This sophisticated sensor has also been used in strategies of self-regulation that have shown to improve the handling of fragile objects (Matulevich *et al.*, 2013). This supports the author's argument that prosthetic hardware is currently beyond our capabilities to naturally interface it with user, because although these strategies are practical and useful, the user continues to receive no tactile information.

Efforts to provide tactile feedback have been mostly focused on sensory substitution (Antfolk *et al.*, 2013), which means that the stimulation is perceived proximally in anatomically incorrect locations (*e.g.,* forearm rather than finger tips), and mostly with a

[10] *E.g.*, Bebionic 3 by RSL steeper, i-limb ultra by Touch Bionics, SensonHand Speed by Ottobock.

different quality. Superficial vibro- or electro-tactile stimulation in the stump regulated by force or position sensors in the terminal device (*e.g.* prosthetic hand) have shown to improve prosthetic control (Dietrich *et al.*, 2012; Witteveen *et al.*, 2012). Despite their potential utility, these approaches have been less clinically successful than self-regulation, as the latter is the only one currently in use. A reason for this might be due to reliability problems on the feedback actuators. To this end, a simple and ingenious solution has been proposed by Antfolk *et al.* (2012), in which pressure is transferred from the prosthetic fingers to the stump via silicone pads filled with air, and thus when the sensor-bulb is compressed, its corresponding terminal in the tactile display expands proportionally. Although not yet in clinical use, this approach seems promising due to its simplicity and so far demonstrated effectiveness at translating tactile information.

Sensory substitution via superficial stimulation is experimentally easier to achieve than approaches aiming to mimic the biological sensors and provide more natural and distally referred perception. However, physiologically appropriate sensory feedback has been argued to drive perceptual shift towards embodiment of the prosthesis, which is fundamental for an image of intact-self (Marasco *et al.*, 2011). Additionally, no training is required as the perception is somatotopically matched, as opposed to sensory substitution. A non-invasive solution to this end is to utilize mechano- and vibro-tactile stimulation in phantom maps (Antfolk *et al.*, 2012), which are rare, variable, and mostly incomplete, and thus not a possibility for all amputees. Another option is the use of the same type of superficial stimulation and TMR, which has resulted in sensory reinnervation (Kuiken *et al.*, 2007a, 2007b). A downside of this approach is that the resulting phantom map is rather random (Figure 21), and thus not all functionally relevant locations and sensations might be available.

Direct stimulation of afferent fibers, or the somatosensory cortex itself, has been long thought as a solution for an intuitive sensory feedback. In the 1970's, a series of patients where fitted with a body power prosthesis instrumented with a strain gauge from which force was translated into frequency of extraneural stimulation pulses (Clippinger *et al.*, 1974). Patients reported to discriminate different level of force and the consistency of objects (soft, resilient, and hard), and although the perception was distally referred (mostly), the quality was described as unnatural (paresthesia). Although this pioneering work demonstrated the feasibility of such approach decades ago, today it is not clinically available, arguably due to the problems related to human-machine communication (see Human-Machine Communication section). Since then, a variety of short-term experiments have continued to show the feasibility of direct neurostimulation to discriminate information such as force and joint angle (Dhillon and Horch, 2005; Horch *et al.*, 2011; Mabuchi, 2013; Raspopovic *et al.*, 2014), with two exceptions, a one year study using percutaneous leads (Tan *et al.*, 2013), and the work reported in Paper V. For historical and contemporary reviews in prosthetics sensory feedback see references (Clippinger *et al.*, 1974; Johansson and Flanagan, 2009; Weber *et al.*, 2012; Antfolk *et al.*, 2013).

Recent and more sophisticated technologies such as optogenetics have clear potential on allowing selective stimulation (Boyden *et al.*, 2005). However, this exciting approach still faces the strict regulatory challenges before translation into clinical applicability (Borton *et al.*, 2013b).

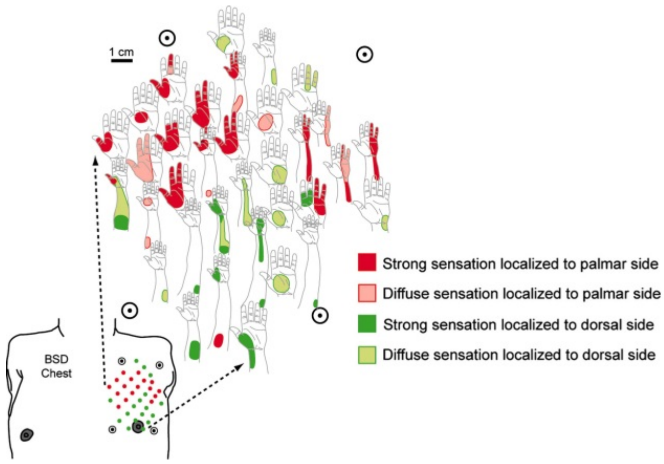

Figure 21. Phantom map after sensory reinnervation in patient BSD. Illustration published in the open access article: Kuiken *et al.*, (2007a), Copyright (2007) National Academy of Sciences, U.S.A.

Summary of the Publications

I - Implantable neuromuscular interfaces: Review with clinical focus

In Paper I, different electrodes technologies with special emphasis on their clinical application in prosthetic control were reviewed from the scientific literature. The practical problems related to surface electrodes were summarized and weighted against the possible complications of their implanted counterparts. Advantages and disadvantages of muscular versus neural interfaces were discussed. This work provides a reference for the clinical viability of intra-/extra- muscular/neural electrodes by summarizing relevant findings on safety and long-term stability, as well as their proven capabilities for recordings and stimulation. This study was instrumental to the selection of epimysial and cuff electrodes as currently the better characterized and most used implantable electrodes in humans, thus providing the support necessary for their permanent implantation in Paper V. Additionally, cuff electrodes were further optimized as a neural recording interface in Paper II.

II – Increasing information content and SNR in extraneural recordings

As found in Paper I, cuff electrodes are currently the most clinically used neural interface. Neurostimulation has been its main application, whereas interfering noise has been a major limitation when used as a recording interface. This is mostly due to the low signal-to-noise ratio (SNR) achieved in extraneural recordings. Ring tripolar configurations have shown to increase the SNR at the cost of providing a single information channel. In Paper II, the effect on SNR of splitting the ring contacts as an attempt to extract more information within the same cuff was investigated.

Different recording configurations with ring and discrete contacts were studied *in vitro* using the frog's sciatic nerve. Compound action potentials were elicited via neurostimulation and recorded together with the stimulation artifact. Myoelectric noise was simulated as a sinusoidal signal induced in the medium at amplitude sufficiently high to be recorded by all configurations, and thus used for SNR comparison. A common configuration to all electrodes allowed normalizing the inter-session experimental differences.

Splitting all ring contacts was found to have a negative effect on the SNR against stimulation artifacts and myoelectric interference, however, if only the central contact of the tripole was divided into discrete contacts, a considerable and statistically significant improvement was found. Additionally, the *in vitro* model employed in this study showed comparable results to those obtained using chronic implantation in mammals, thus suggesting a simplified method to conduct related investigations.

The results from this study suggest that any tripolar configuration benefits from splitting the central ring contact when considering for higher SNR and additional channels of information. Both of these factors are relevant to the utilization of cuff electrodes as recording neural interfaces. Furthermore, having discrete contacts also increases the number of channels for stimulation, and thus creates the possibility to elicit perception in different projected locations, as demonstrated in Paper V.

III - BioPatRec

Paper III introduced an open source research platform for development and benchmarking of advanced prosthetic control strategies based on pattern recognition (BioPatRec). The motivations for this work were 1) the impossibility to compare the wealth of algorithms proposed for prosthetic control, mainly due to the number of inter-study dependent variables; 2) foster collaboration, allow repeatability, and possibly reduce unnecessary repetition of common code; and 3) the creation of a common repository of bioelectric signals related to limb motions.

BioPatRec allows a seamless implementation of algorithms in the fields of signal processing; feature selection and extraction; pattern recognition; and, real-time control. It is the first open source platform that includes all the necessary routines for the control of a virtual arm with a variety of the algorithms in the aforementioned fields.

Three pattern recognition algorithms were compared in real-time, including a new paradigm based on negative feedback. Additionally to the traditional performance metrics by the motion tests, *real-time accuracy* was introduced. The results indicate that algorithms with similar offline accuracy can produce contrasting real-time results, thus stressing the need for real-time evaluations. Two of such real-time evaluations are provided in BioPatRec (Motion and Target Achievement Control tests), including a virtual arm. One year after its release in February 2013, BioPatRec has been downloaded over 160 times and it has been personally shared by the author to 10 researchers in 8 countries.

BioPatRec offers the first open repository of bioelectric signals related to limb motions. It initially provided recordings from 20 subjects executing 10 individual movements (Paper

III), and consequently 17 subjects executing simultaneous motions in 3 DoF for a total of 26 movements (Paper IV). More importantly, the online hosting platform allows for any person to contribute to this repository, in which neuroelectric signals will be also included in the future.

IV – Simultaneous and real-time prosthetic control

In paper IV we demonstrated that a variety of pattern recognition algorithms can successfully predict simultaneous movements if arranged in dedicated topologies, or provided with a proper problem transformation. The performance of such strategies was evaluated for real-time prediction and controllability, as opposed to exclusively offline accuracy as previously done. A floor-noise strategy was implemented to reduce misclassification during transient periods between *rest* (no motion) and the desired movement. The strategies presented in this study require solely myoelectric signals as the input information, thus they are applicable to bilateral amputees and more practical for the clinical setting, as no other sensing hardware is required (*e.g.*, motion compute or force measuring hardware). It was demonstrated that simultaneous MPR produced a higher controllability over individual MPR when used in a target acquisition test based on virtual reality.

V - The osseointegrated human-machine gateway (OHMG)

The concept and clinical implementation of the OHMG is presented in Paper V. Epimysial and cuff electrodes were permanently implanted in a transhumeral patient who had received an osseointegrated implant (OPRA) for direct skeletal attachment of his arm prosthesis 3 years earlier. His implant was upgraded with custom made components that allowed for feedthrough electrical communication to the implanted electrodes. No complications have been reported at 15 months follow up.

The patient was fitted with an analog controller for his conventional myoelectric prosthesis using the epimysial electrodes as the source for control. This system has been used by the patient in daily and professional activities uninterruptedly for over one year, making him the first patient in modern times to receive permanently implanted electrodes as source for prosthetic control in activities of the daily living.

Improved controllability was observed in function of grip resolution and force; reduced muscular effort; increased comfort; and resilience to motion artifacts, limb position, and environmental conditions. All these improvements resulted in increased prosthetic use and wearing time.

Intuitive control of additional degrees of freedom (DoF) was shown possible via myoelectric pattern recognition (MPR) for up to 4 DoF offline, and evaluated in real-time for 3 DoF available in commercial prostheses. It was found that epimysial electrodes produced the same or higher accuracy than surface electrodes located in an equivalent location. Additionally, we found that classifiers can produce similar real-time performance after 3 months without retraining when fed by the epimysial electrodes, thus additionally demonstrating the long-term stability of the implemented control source.

Direct nerve stimulation via the cuff electrode was used to elicit appropriate sensory perception. A single asymmetric balanced pulse produced consistent sensory perception in quality, intensity, and projected locations for 8 months, thus demonstrating the feasibility of a long-term implementation of intuitive and distally referred sensory feedback.

Summary of the Thesis Contributions

Despite the stride made in the field of artificial limbs using neuromuscular interfaces and osseointegration, these technologies have not previously been combined in a meaningful way for patients until this work, which is the major contribution of this doctoral thesis (Paper V). Additional conclusive results and contributions of this thesis are:

- It was demonstrated that consistent tactile perception (quality, magnitude, and localized projection) can be chronically reproduced (> 8 months) via direct electrical stimulation of severed peripheral nerves, and despite a long-term amputation (> 10 years) - Paper V.
- It was demonstrated that an improved prosthetic control resolution and resilience to motion artifacts, limb position, and environmental conditions is achieved, when epimysial as opposed to surface electrodes were employed as the source of control (Paper V).
- Accurate prediction of hand and wrist movements from more proximal muscles such as biceps and triceps was demonstrated. More importantly, it was shown that the classifier performance remains consistent after long periods of time without retraining (3 months), thus demonstrating the long-term stability of myoelectric signals recorded by epimysial electrodes (Paper V).
- Simultaneous and real-time control with a variety of pattern recognition algorithms and topologies was demonstrated. It was shown that practically any pattern recognition algorithm can be successful in this task if arranged in a dedicated topology, or using the *label power set* transformation (Paper IV). The presented strategies do not require additional hardware other than EMG acquisition, and they are applicable to bilateral amputees.
- It was demonstrated the simultaneous MPR improves controllability over sequential control when tested in a virtual limb (Paper IV).
- It was found that classifiers can deliver considerably different real-time performance despite having similar offline accuracy. This suggests that there is no clear rule on how a given prediction strategy will perform in real-time based solely on offline accuracy, and therefore the real-time testing must be seen as a requirement in further work (Paper III).

- The first open source platform for the development and benchmarking of advanced prosthetic control strategies based on pattern recognition algorithms was released for public use (Paper III).
- The largest data sets used in any published MPR study were released in an open access repository. Recordings from individual (Paper III) and simultaneous movements are provided (Paper IV).
- It was found that splitting the central ring contract in tripolar configurations improve the signal-to-noise ratio and increase the number of information channels (Paper II).
- A convenient methodological *in vitro* approach is proposed which eliminates the need of chronic implantations when studying improvement ratios of extraneural interference rejection in neural recordings (Paper II).
- A review of the clinical relevance of implanted neuromuscular interfaces for prosthetic control was conducted (Paper I).

Despite that the work conducted in this thesis was focused in upper limbs, the developments and discoveries presented here can also be applied to lower limbs. However, the lack of commercially available lower limb prostheses driven by myoelectric signals will probable slow down the translation of this research to lower limb prosthetics. In a similar way, even though this thesis had a focus on electrodes at the peripheral nerves and muscles, BMIs could also be interfaced with the artificial limb via the OHMG.

Conclusion and Future Work

A summary of the latest upper limb prosthetic technologies in research laboratories around the world has been presented in the framework of this thesis. Promising and exciting developments are ongoing worldwide. Unfortunately for patients, the current clinical reality is that the majority of upper limb amputees do not even wear a myoelectric prosthesis (Kyberd *et al.*, 2007), although this is presently the most sophisticated solution available. There is a variety of reasons for why patients would choose not to use myoelectric or any type of prostheses at all. Socket problems, poor functionality, and lack of sensory feedback have been found as the main complains with prosthetic devices. Not surprisingly, patients that have reported to use their prostheses the least, also reported to be mainly dissatisfied with the prosthesis functionality and socket suspension (Kyberd *et al.*, 2007).

The use of osseointegration alone has several benefits amounting to an improve quality of life (Brånemark *et al.*, 2014), some of which are improved functionality and sensory feedback, aside eliminating socket related problems. The work realized in this thesis has expanded in this technology to address prosthetic control sourced by implanted neuromuscular interfaces via a permanent and bidirectional osseointegrated human-machine gateway.

The implications to reliably access implanted electrodes for the control of artificial limbs can only be understood when carefully examining the current clinical reality, which has not considerably improved after decades of research on advanced prosthetic control strategies (Farina *et al.*, 2014). Therefore the author considers the technology presented here as a necessary step towards the clinical implementation of such advanced prosthetic control strategies, including appropriate sensory feedback. This and the clinical trial of the OHMG are logic continuation steps from this work. Ongoing efforts are dedicated to the creation of an artificial limb controller (ALC) to be embedded in the prosthetic limb. The ALC must provide enough processing power to execute pre- and post-processing algorithms, as well as the pattern recognition, control, and monitoring (Figure 22). In parallel, a user-friendly computer program is currently under evaluation by our group, where the patient can safely train advanced prosthetic control strategies using augmented reality at home. On the sensory side, current work is conducted for a more detailed understanding of the long-term psychophysics resulting from extraneural stimulation, which findings will be eventually implemented in a sensory feedback system connected to the ALC.

Finally, while the current tradeoff between the risks associated with osseointegrated percutaneous implants, and the functionality restored by this technology, is in favor of the solution presented here, there are always rooms for improvements. Therefore, additional strategies for infection control are currently explored by our group to further improve the percutaneous interface.

All the aforementioned current and future work is clear indications of the efforts still required if artificial limbs are expected to one day satisfactorily restore the functionality lost by an amputation.

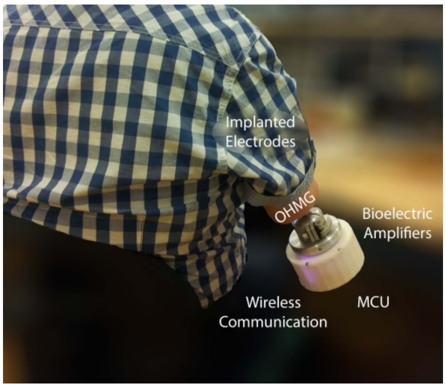

Figure 22. Implanted electrodes are accessed via the osseointegrated human-machine gateway (OHMG) from which amplifiers and acquisition electronics feed the bioelectric signals to a microcontroller (MCU). This prototype is the foundation for a future artificial limb controller (ALC), which will be embedded in the prosthetic device. The wireless interface was implemented for electrical isolation as a safety measure during unsupervised operation at home, as this system can also be used for practicing on advanced prosthetic control strategies using a virtual limb.

References

Ackerley, R., Wasling, H. B., Liljencrantz, J., Olausson, H., Johnson, R. D., and Wessberg, J. (2014). Human C-Tactile Afferents Are Tuned to the Temperature of a Skin-Stroking Caress. *J Neurosci* 34, 2879–2883.

Adams, P., Hendershot, G., and Marano, M. (1999). Current estimates from the National Health Interview Survey, 1996. *Vital Heal Stat 10* 200, 1–203.

Affeld, K., Grosshauser, J., Goubergrits, L., and Kertzscher, U. (2012). Percutaneous devices: a review of applications, problems and possible solutions. *Expert Rev Med Devices* 9, 389–99.

Ajiboye, A. B., and Weir, R. F. (2009). Muscle synergies as a predictive framework for the EMG patterns of new hand postures. *J Neural Eng* 6, 036004.

Al-Ajam, Y., Lancashire, H., Pendegrass, C., Kang, N., Dowling, R. P., Taylor, S. J. G., and Blunn, G. (2013). The use of a bone-anchored device as a hard-wired conduit for transmitting EMG signals from implanted muscle electrodes. *IEEE Trans Biomed Eng* 60, 1654–9.

Almström, C., Herberts, P., and Körner, L. (1981). Experience with Swedish multifunctional prosthetic hands controlled by pattern recognition of multiple myoelectric signals. *Int. Orthop.* 5, 15–21.

Al-Timemy, A. H., Member, S., Bugmann, G., Escudero, J., and Outram, N. (2013). Classification of finger movements for the dexterous hand prosthesis control with surface electromyography. *IEEE J. Biomed. Heal. Informatics* 17, 608–618.

Ameri, A., Scheme, E., Kamavuako, E., Englehart, K., and Parker, P. (2014). Real Time, Simultaneous Myoelectric Control Using Force and Position Based Training Paradigms. *IEEE Trans Biomed Eng* 61, 279–287.

Amsuss, S., Gobel, P., Jiang, N., Graimann, B., Paredes, L., and Farina, D. (2014). Self-Correcting Pattern Recognition System of Surface EMG Signals for Upper Limb Prosthesis Control. *IEEE Trans Biomed Eng* 61, 1167–1176.

Anani, A. B., Ikeda, K., and Körner, L. M. (1977). Human ability to discriminate various parameters in afferent electrical nerve stimulation with particular reference to prostheses sensory feedback. *Med Biol Eng Comput* 15, 363–73.

Andrade, A. O., Pereira, A. a., Walter, S., Almeida, R., Loureiro, R., Compagna, D., and Kyberd, P. J. (2014). Bridging the gap between robotic technology and health care. *Biomed. Signal Process. Control* 10, 65–78. Available at: http://linkinghub.elsevier.com/retrieve/pii/S1746809413001845

Antfolk, C., Björkman, A., Frank, S.-O., Sebelius, F., Lundborg, G., and Rosen, B. (2012). Sensory feedback from a prosthetic hand based on air-mediated pressure from the hand to the forearm skin. *J Rehabil Med* 44, 702–7.

Antfolk, C., D'Alonzo, M., Rosén, B., Lundborg, G., Sebelius, F., and Cipriani, C. (2013). Sensory feedback in upper limb prosthetics. *Expert Rev Med Devices* 10, 45–54.

Asplund, M., Nilsson, M., Jacobsson, A., and von Holst, H. (2009). Incidence of traumatic peripheral nerve injuries and amputations in Sweden between 1998 and 2006. *Neuroepidemiology* 32, 217–228.

Atkins, D. J., Heard, D. C. Y., and Donovan, W. H. (1996). Epidemiologic overview of individuals with upper-limb loss and their reported research priorities. *J Prosthet Orthot* 8.

Axelsson, M., Dang, Q., Pitsillides, K., Munns, S., Hicks, J., and Kassab, G. S. (2007). A novel, fully implantable, multichannel biotelemetry system for measurement of blood flow, pressure, ECG, and temperature. *J. Appl. Physiol.* 102, 1220–8.

Baker, J. J., Scheme, E. J., Englehart, K., Hutchinson, D. T., and Greger, B. (2010). Continuous detection and decoding of dexterous finger flexions with implantable myoelectric sensors. *IEEE Trans Neural Syst Rehabil Eng* 18, 424–32.

Barone, U., and Merletti, R. (2013). Design of a portable, intrinsically safe multichannel acquisition system for high-resolution, real-time processing HD-sEMG. *IEEE Trans Biomed Eng* 60, 2242–2252.

Ben-Menachem, E., Rydenhag, B., and Silander, H. (2013). Preliminary experience with a new system for vagus nerve stimulation for the treatment of refractory focal onset seizures. *Epilepsy Behav.* 29, 416–9.

Bensmaia, S. J., and Miller, L. E. (2014). Restoring sensorimotor function through intracortical interfaces: progress and looming challenges. *Nat. Rev. Neurosci.* 15, 313–325.

Borton, D. A., Yin, M., Aceros, J., and Nurmikko, A. (2013a). An implantable wireless neural interface for recording cortical circuit dynamics in moving primates. *J Neural Eng* 10.

Borton, D., Micera, S., Millán, J. D. R., and Courtine, G. (2013b). Personalized neuroprosthetics. *Sci. Transl. Med.* 5.

Boyden, E. S., Zhang, F., Bamberg, E., Nagel, G., and Deisseroth, K. (2005). Millisecond-timescale, genetically targeted optical control of neural activity. *Nat. Neurosci.* 8, 1263–8.

Brånemark, P.-I. (1993). Holding means and methods of implantation thereof in osseous tissue. United States Patent 5,562,670.

Brånemark, P.-I. (1959). Vital microscopy of bone marrow in rabbit. *Scand J Clin Lab Invest* 38.

Brånemark, P.-I., Hansson, B. O., Adell, R., Breine, U., Lindström, J., Hallen, O., and Öhman, A. (1977). Osseointegrated implants in the treatment of the edentulous jaw. *Scand J Plast Reconstr Surg Suppl* 16, 1–132.

Brånemark, R., Berlin, Ö., Hagberg, K., Bergh, P., Gunterberg, B., and Rydevik, B. (2014). A novel osseointegrated, percutaneous prosthetic system for treatment of patients with transfemoral amputation: A prospective study of 51 patients. *Bone Jt. J* 96-B, 106–113.

Brånemark, R., Brånemark, P.-I., Rydevik, B., and Myers, R. R. (2001). Osseointegration in skeletal reconstruction and rehabilitation: A review. *J Rehabil Res Dev* 38, 175–81.

Brånemark, R., Emanuelsson, L., Palmquist, A., and Thomsen, P. (2011). Bone response to laser-induced micro- and nano-size titanium surface features. *Nanomedicine* 7, 220–7.

Bunderson, N. E., and Kuiken, T. (2012). Quantification of feature space changes with experience during electromyogram pattern recognition control. *IEEE Trans Neural Syst Rehabil Eng* 20, 239–46.

Camacho, G. A., Llanos, C. H., Berger, P. A., Miosso, C. J., and Rocha, A. F. (2013). An experimental evaluation of the incidence of on the classification performance of myoelectric control systems with iPCA tuning. *Biomed Eng Online* 12, 133.

Chan, A. D. C., and Englehart, K. B. (2005). Continuous myoelectric control for powered prostheses using hidden Markov models. *IEEE Trans Biomed Eng* 52, 121–124..

Chan, A. D. C., and Lemaire, E. D. (2010). Flexible dry electrode for recording surface electromyogram. in *2010 IEEE Instrumentation & Measurement Technology Conference Proceedings*, 1234–1237.

Cheung, K. C. (2007). Implantable microscale neural interfaces. *Biomed. Microdevices* 9, 923–38.

Cipriani, C., Antfolk, C., Controzzi, M., Lundborg, G. N., Rosen, B., Carrozza, M. C., and Sebelius, F. (2011). Online myoelectric control of a dexterous hand prosthesis by transradial amputees. *IEEE Trans Neural Syst Rehabil Eng* 19, 260–70.

Clippinger, F., Avery, R., and Titus, B. (1974). A sensory feedback system for an upper-limb amputation prosthesis. *Bull. Prosthet. Res.* 10-22, 247–258.

Clippinger, F. W., McElhaney, J. H., Maxwell, M. G., Vaughn, D. W., Horton, G., and Bright, L. (1981). Prosthetic sensory feedback lower extremity. *Newsl. Prosthetics Orthot. Clin.* 5, 1–3. Available at: http://oandplibrary.com/cpo/pdf/1981_03_001.pdf [Accessed August 18, 2013].

Collinger, J. L., Wodlinger, B., Downey, J. E., Wang, W., Tyler-kabara, E. C., Weber, D. J., Mcmorland, A. J. C., Velliste, M., Boninger, M. L., and Schwartz, A. B. (2012). High-performance neuroprosthetic control by an individual with tetraplegia. *Lancet* 6736, 1–8. Available at: http://dx.doi.org/10.1016/S0140-6736(12)61816-9.

Delbeke, J. (2011). Electrodes and chronic optic nerve stimulation. *Biocybern. Biomed. Eng.* 31, 81–94.

Dhillon, G. S., and Horch, K. W. (2005). Direct neural sensory feedback and control of a prosthetic arm. *IEEE Trans Neural Syst Rehabil Eng* 13, 468–72.

Dhillon, G. S., Krüger, T. B., Sandhu, J. S., and Horch, K. W. (2005). Effects of short-term training on sensory and motor function in severed nerves of long-term human amputees. *J Neurophysiol 93*, 2625–33.

Dhillon, G. S., Lawrence, S. M., Hutchinson, D. T., and Horch, K. W. (2004). Residual function in peripheral nerve stumps of amputees: implications for neural control of artificial limbs. *J Hand Surg* 29, 605–15; discussion 616–18.

Dietrich, C., Walter-Walsh, K., Preissler, S., Hofmann, G. O., Witte, O. W., Miltner, W. H. R., and Weiss, T. (2012). Sensory feedback prosthesis reduces phantom limb pain: proof of a principle. *Neurosci. Lett.* 507, 97–100.

Dillingham, T., Pezzin, L., MacKenzie, E., and Burgess, A. (2001). Use and Satisfaction with Prosthetic Devices Among Persons with Trauma-Related Amputations: A Long-Term Outcome Study. *Am J Phys Med Rehabil* 80, 563–571.

Dubernard, J.-M., Owen, E., Herzberg, G., Lanzetta, M., Martin, X., Kapila, H., Dawahra, M., and Shakim, N. S. (1999). Human Hand Allograft: Report on First 6 Months. *Lancet* 353, 1315–1320.

Dudek, N. L., Marks, M. B., Marshall, S. C., and Chardon, J. P. (2005). Dermatologic conditions associated with use of a lower-extremity prosthesis. *Arch Phys Med Rehabil* 86, 659–663.

Dun, C. A. J., Faber, H. T., de Wolf, M. J. F., Mylanus, E. A. M., Cremers, C. W. R. J., and Hol, M. K. S. (2012). Assessment of more than 1,000 implanted percutaneous bone conduction devices: skin reactions and implant survival. *Otol. Neurotol.* 33, 192–8.

Elliott, R. M., Tintle, S. M., and Levin, L. S. (2013). Upper extremity transplantation: current concepts and challenges in an emerging field. *Curr Rev Musculoskelet Med* 7, 83–8.

Englehart, K., and Hudgins, B. (2003). A robust, real-time control scheme for multifunction myoelectric control. *IEEE Trans Biomed Eng* 50, 848–54.

Englehart, K., Hudgins, B., Parker, P., and Stevenson, M. (1999). Classification of the myoelectric signal using time-frequency based representations. *Med. Eng. Phys.* 21, 431–8.

Eriksson, L., Sebelius, F., and Balkenius, C. (1998). Neural control of a virtual prosthesis. in *Proc. ICANN98, the 8th International Conference on Artificial Neural Networks*, eds. L. Niklasson, M. Boden, and T. Ziemke (Springer London), 905–910. Available at: http://www.lucs.lu.se/christian.balkenius/pdf/Eriksson.Sebelius.Balkenius.1998.Prosthesis.ICANN.pdf.

Farfán, F. D., Politti, J. C., and Felice, C. J. (2010). Evaluation of EMG processing techniques using Information Theory. *Biomed Eng Online* 9, 72.

Farina, D., Jiang, N., Rehbaum, H., Holobar, A., Graimann, B., Dielt, H., and Aszmann, O. (2014). The Extraction of Neural Information from the Surface EMG for the Control of Upper-Limb Prostheses: Emerging Avenues and Challenges. *IEEE Trans Neural Syst Rehabil Eng,* advance online publication http://ieeexplore.ieee.org/lpdocs/epic03/wrapper.htm?arnumber=6737308.

Farina, D., and Negro, F. (2012). Accessing the neural drive to muscle and translation to neurorehabilitation technologies. *IEEE Rev. Biomed. Eng.* 5, 3–14.

Farrell, T. R., and Weir, R. F. F. (2008). A comparison of the effects of electrode implantation and targeting on pattern classification accuracy for prosthesis control. *IEEE Trans Biomed Eng* 55, 2198–211.

Finch, J. L., Heath, G. H., David, A. R., and Kulkarni, J. (2012). Biomechanical Assessment of Two Artificial Big Toe Restorations From Ancient Egypt and Their Significance to the History of Prosthetics. *J Prosthet Orthot* 24, 181–191.

Finley, F., and Wirta, R. (1967). Myocoder-computer study of electromyographic patterns. *Arch Phys Med Rehabil* 48, 20–4.

Fishel, J. A., and Loeb, G. E. (2012). Sensing tactile microvibrations with the BioTac—Comparison with human sensitivity. in *4th IEEE RAS & EMBS Int Conf Biomed Robotics Biomecha* (Roma), 1122–1127. Available at: http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=6290741.

Fougner, A., Scheme, E., Chan, A. D. C., Englehart, K., and Stavdahl, O. (2011). Resolving the limb position effect in myoelectric pattern recognition. *IEEE Trans Neural Syst Rehabil Eng* 19, 644–51.

Frossard, L., Hagberg, K., Häggström, E., Gow, D. L., Brånemark, R., and Pearcy, M. (2010). Functional Outcome of Transfemoral Amputees Fitted With an Osseointegrated Fixation: Temporal Gait Characteristics. *J Prosthet Orthot* 22, 11–20. Available at: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00008526-201001000-00003.

Gailey, R., Allen, K., Castles, J., Kucharik, J., and Roeder, M. (2008). Review of secondary physical conditions associated with lower-limb amputation and long-term prosthesis use. *J Rehabil Res Dev* 45, 15–29.

Geddes, L. a., and Roeder, R. (2003). Criteria for the Selection of Materials for Implanted Electrodes. *Ann. Biomed. Eng.* 31, 879–890. Available at: http://link.springer.com/10.1114/1.1581292.

Geng, Y., Zhang, L., Tang, D., Zhang, X., and Li, G. (2013). Pattern recognition based forearm motion classification for patients with chronic hemiparesis. in *35th Ann Int Conf IEEE EMBS* (Osaka), 5918–21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24111086.

Geng, Y., Zhou, P., and Li, G. (2012). Toward attenuating the impact of arm positions on electromyography pattern-recognition based motion classification in transradial amputees. *J Neuroengineering Rehabil* 9, 74.

Gilbert, R. (1964). Transplant is successful with a cadaver forearm. *Med Trib Med News* 2, 20–3.

Graupe, D. (1974). Control of upper-limb prostheses in several degrees of freedom. *Bull Prosthet Res* 11, 226–236.

Graupe, D., Cline, W. K., and Kaplon, T. K. (1973). Stochastic analysis of EMG signals for multi-functional prosthesis control purposes. in *Proc. 1973 Canahan Conf. on Electronic Prosthetics* (Lexington, KY).

Guo, J.-Y., Zheng, Y.-P., Xie, H.-B., and Koo, T. K. (2013). Towards the application of one-dimensional sonomyography for powered upper-limb prosthetic control using machine learning models. *Prosthet Orthot Int* 37, 43–9.

Guyon, I., and Elisseeff, A. (2003). An introduction to variable and feature s election. *J. Mach. Learn. Res.* 3, 1157–1182.

Hagberg, K., and Brånemark, R. (2001). Consequences of non-vascular trans-femoral amputation: a survey of quality of life, prosthetic use and problems. *Prosthet Orthot Int* 25, 186–94. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11860092.

Hagberg, K., and Brånemark, R. (2009). One hundred patients treated with osseointegrated transfemoral amputation prostheses—rehabilitation perspective. *J Rehabil Res Dev* 46, 331–344. Available at: http://www.biomedsearch.com/article/One-hundred-patients-treated-with/214103137.html.

Hagberg, K., Brånemark, R., Gunterberg, B., and Rydevik, B. (2008). Osseointegrated trans-femoral amputation prostheses: prospective results of general and condition-specific quality of life in 18 patients at 2-year follow-up. *Prosthet Orthot Int* 32, 29–41.

Hagberg, K., Häggström, E., Uden, M., and Brånemark, R. (2005). Socket versus bone-anchored trans-femoral prostheses: Hip range of motion and sitting comfort. *Prosthet Orthot Int* 29, 153–163. Available at: http://poi.sagepub.com/lookup/doi/10.1080/03093640500238014.

Hahne, J. M., Bießmann, F., Jiang, N., Rehbaum, H., Farina, D., Meinecke, F. C., Müller, K., and Parra, L. C. (2014). Linear and Nonlinear Regression Techniques for Simultaneous and Proportional Myoelectric Control. 22, 269–279.

Hankin, D., Hansen, M., and Lockhart, J., Direct and Intuitive Prosthetic Control with a Leaded Myoelectric Sensor (LIMES) System (2014), presentation at *DARPA Sensorimotor Prosthetic Workshop / RE-NET Program Review*, Phoenix, AZ, Feb 12-13, 2014.

Hargrove, L. J., Englehart, K., and Hudgins, B. (2007). A comparison of surface and intramuscular myoelectric signal classification. *IEEE Trans Biomed Eng* 54, 847–53.

Hargrove, L. J., Lock, B. A., and Simon, A. M. (2013a). Pattern Recognition Control Outperforms Conventional Myoelectric Control in Upper Limb Patients with Targeted Muscle Reinnervation. in *35th Ann Int Conf IEEE EMBS* (Osaka), 1599–1602.

Hargrove, L. J., Scheme, E. J., Englehart, K. B., and Hudgins, B. S. (2010). Multiple binary classifications via linear discriminant analysis for improved controllability of a powered prosthesis. *IEEE Trans Neural Syst Rehabil Eng* 18, 49–57.

Hargrove, L. J., Simon, A. M., Young, A. J., Lipschutz, R. D., Finucane, S. B., Smith, D. G., and Kuiken, T. A. (2013b). Robotic Leg Control with EMG Decoding in an Amputee with Nerve Transfers. *N Engl J Med* 369, 1237–42.

Hart, R. L., Bhadra, N., Montague, F. W., Kilgore, K. L., and Peckham, P. H. (2011). Design and testing of an advanced implantable neuroprosthesis with myoelectric control. *IEEE Trans Neural Syst Rehabil Eng* 19, 45–53.

Haugland, M., and Sinkjaer, T. (1995). Cutaneous whole nerve recordings used for correction of footdrop in hemiplegic man. *IEEE Trans Rehabil Eng* 3, 307–317.

Herberts, P., Almström, C., and Caine, K. (1978). Clinical application study of multifunctional prosthetic hands. *J Bone Jt. Surg* 60, 552–560.

Herberts, P., Almström, C., Kadefors, R., and Lawrence, P. D. (1973). Hand prosthesis control via myoelectric patterns. *Acta Orthop. Scand.* 44, 389–409.

Herberts, P., Kadefors, R., Kaiser, E., and Petersen, I. (1968). Implantation of micro-circuits for myo-electric control of prostheses. *J Bone Jt Surg* 50, 780–791. Available at: http://www.bjj.boneandjoint.org.uk/content/50-B/4/780.full.pdf.

Ho, T. K., Basu, M., Hiu, M., and Law, C. (2006). "Measures of Geometrical Complexity in Classification," in *Data Complexity in Pattern Recognition*, eds. M. Basu and T. Ho (London: Springer), 1–23. Available at: http://dx.doi.org/10.1007/978-1-84628-172-3_1.

Hochberg, L. R., Serruya, M. D., Friehs, G. M., Mukand, J. a, Saleh, M., Caplan, A. H., Branner, A., Chen, D., Penn, R. D., and Donoghue, J. P. (2006). Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature* 442, 164–71.

Hoffer, J. a, Stein, R. B., Haugland, M. K., Sinkjaer, T., Durfee, W. K., Schwartz, a B., Loeb, G. E., and Kantor, C. (1996). Neural signals for command control and feedback in functional neuromuscular stimulation: a review. *J Rehabil Res Dev* 33, 145–57.

Hoffer, J., and Loeb, G. E. (1980). Implantable electrical and mechanical interfaces with nerve and muscle. *Ann. Biomed. Eng.* 8, 351–60.

Horch, K., Meek, S., Taylor, T. G., and Hutchinson, D. T. (2011). Object discrimination with an artificial hand using electrical stimulation of peripheral tactile and proprioceptive pathways with intrafascicular electrodes. *IEEE Trans Neural Syst Rehabil Eng* 19, 483–9.

Hoshiyama, M., Kakigi, R., and Nagata, O. (1999). Peripheral nerve conduction recorded by a micro gradiometer system (micro-SQUID) in humans. *Neurosci. Lett.* 272, 199–202.

Huang, G., Zhang, Z., Zhang, D., and Zhu, X. (2013). Spatio-spectral filters for low-density surface electromyographic signal classification. *Med. Biol. Eng. Comput.* 51, 547–55.

Huang, H., and Kuiken, T. (2009). A Strategy for Identifying Locomotion Modes Using Surface Electromyography. *IEEE Trans Biomed Eng* 56, 65–73.

Huang, H., Zhou, P., Li, G., and Kuiken, T. (2009). Spatial filtering improves EMG classification accuracy following targeted muscle reinnervation. *Ann. Biomed. Eng.* 37, 1849–57.

Huang, Y., Englehart, K., Hudgins, B., and Chan, A. D. C. (2005). A Gaussian mixture model based classification scheme for myoelectric control of powered upper limb prostheses. *IEEE Trans Biomed Eng* 52, 1801–1811.

Håkansson, B., Tjellström, A., Rosenhall, U., and Carlsson, P. (1985). The bone-anchored hearing aid. Principal design and a psychoacoustical evaluation. *Acta Otolaryngol* 100, 229–239.

Häggström, E. E., Hansson, E., and Hagberg, K. (2013a). Comparison of prosthetic costs and service between osseointegrated and conventional suspended transfemoral prostheses. *Prosthet Orthot Int* 37, 152–60.

Häggström, E., Hagberg, K., Rydevik, B., and Brånemark, R. (2013b). Vibrotactile evaluation: Osseointegrated versus socket-suspended transfemoral prostheses. *J Rehabil Res Dev* 50, 1423–34. Available at: http://www.rehab.research.va.gov/jour/2013/5010/jrrd-2012-08-0135.html.

Ilizarov, G. A. (1990). Clinical application of the tension-stress effect for limb lengthening. *Clin Orthop Relat Res* 250, 8–26.

Islam, A., Sundaraj, K., Ahmad, B., Ahamed, N. U., and Ali, A. (2012). Mechanomyography sensors for muscle assessment: a brief review. *J Phys Ther Sci* 24, 1359–1365. Available at: http://dspace.unimap.edu.my/xmlui/handle/123456789/33419 [Accessed April 15, 2014].

Jacobs, R., Brånemark, R., Olmarker, K., Rydevik, B., Steenberghe, D. Van, and Brånemark, P. (2000). Evaluation of the psychophysical detection threshold level for vibrotactile and pressure stimulation of prosthetic limbs using bone anchorage or soft tissue support. *Prosthet Orthot Int* 24, 133–142. Available at: http://poi.sagepub.com/lookup/doi/10.1080/03093640008726536.

Jiang, N., Dosen, S., Müller, K.-R., and Farina, D. (2012a). Myoelectric control of artificial limbs: is there the need for a change of focus? *IEEE Signal Process Mag* 29, 148–152.

Jiang, N., Englehart, K. B., and Parker, P. (2009). Extracting simultaneous and proportional neural control information for multiple-DOF prostheses from the surface electromyographic signal. *IEEE Trans Biomed Eng* 56, 1070–80.

Jiang, N., Muceli, S., Graimann, B., and Farina, D. (2013a). Effect of arm position on the prediction of kinematics from EMG in amputees. *Med Biol Eng Comput* 51, 143–51.

Jiang, N., Rehbaum, H., Vujaklija, I., Graimann, B., and Farina, D. (2013b). Intuitive, Online, Simultaneous and Proportional Myoelectric Control Over Two Degrees of Freedom in Upper Limb Amputees. *IEEE Trans Neural Syst Rehabil Eng.*

Jiang, N., Vest-Nielsen, J. L., Muceli, S., and Farina, D. (2012b). EMG-based simultaneous and proportional estimation of wrist/hand dynamics in uni-Lateral trans-radial amputees. *J Neuroengineering Rehabil* 9, 42. Available at: http://www.jneuroengrehab.com/content/9/1/42.

Jiang, N., Vujaklija, I., Rehbaum, H., Graimann, B., and Farina, D. (2013c). Is Accurate Mapping of EMG Signals on Kinematics Needed for Precise Online Myoelectric Control? *IEEE Trans Neural Syst Rehabil Eng.* Available at: http://www.ncbi.nlm.nih.gov/pubmed/24235278.

Johannesson, A. (2009). Lower limb amputation in patients with vascular disease. *Doctoral Thesis*, Dept. of Clinical Sciences, Lund University.

Johansson, R. S., and Flanagan, J. R. (2009). Coding and use of tactile signals from the fingertips in object manipulation tasks. *Nat. Rev. Neurosci.* 10, 345–59.

Jönsson, S., Caine-Winterberger, K., and Brånemark, R. (2011). Osseointegration amputation prostheses on the upper limbs: methods, prosthetics and rehabilitation. *Prosthet Orthot Int* 35, 190–200.

Kaliki, R. R., Davoodi, R., and Loeb, G. E. (2013). Evaluation of a noninvasive command scheme for upper-limb prostheses in a virtual reality reach and grasp task. *IEEE Trans Biomed Eng* 60, 792–802.

Kamavuako, E. N., Scheme, E. J., and Englehart, K. B. (2014). Combined surface and intramuscular EMG for improved real-time myoelectric control performance. *Biomed. Signal Process. Control* 10, 102–107. Available at: http://dx.doi.org/10.1016/j.bspc.2014.01.007.

Kanitz, G., Antfolk, C., and Cipriani, C. (2011). Decoding of individuated finger movements using surface EMG and input optimization applying a genetic algorithm. in *33rd Ann Int Conf IEEE EMBS* (Boston), 1608–1611. Available at: http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=6090465.

Kendell, C., Lemaire, E. D., Losier, Y., Wilson, A., Chan, A., and Hudgins, B. (2012). A novel approach to surface electromyography: an exploratory study of electrode-pair selection based on signal characteristics. *J Neuroengineering Rehabil* 9, 24.

Kilgore, K. L., Hoyen, H. a, Bryden, A. M., Hart, R. L., Keith, M. W., and Peckham, P. H. (2008). An implanted upper-extremity neuroprosthesis using myoelectric control. *J. Hand Surg. Am.* 33, 539–50.

Kilgore, K. L., Peckham, P. H., Keith, M. W., Montague, F. W., Hart, R. L., Gazdik, M. M., Bryden, A. M., Snyder, S. a, and Stage, T. G. (2003). Durability of implanted electrodes and leads in an upper-limb neuroprosthesis. *J Rehabil Res Dev* 40, 457–68. Available at: http://www.rehab.research.va.gov/jour/03/40/6/Kilgore.html.

Kilgore, K. L., Peckham, P. H., Montague, F. W., Hart, R. L., Bryden, A. M., Keith, M. W., Hoyen, H., and Bhadra, N. (2005). An Implanted Upper Extremity Neuroprosthesis Utilizing Myoelectric Control. in *Proc. 2nd Int. IEEE EMBS, Conf. on Neural Engieering* (Arlington), 368–371. Available at: http://ieeexplore.ieee.org/lpdocs/epic03/wrapper.htm?arnumber=1419634.

Klineberg, I., Calford, M., Dreher, B., Henry, P., Macefield, V., Miles, T., Rowe, M., Sessle, B., and Trulsson, M. (2005). A Consensus Statement on Osseoperception. *Clin Exp Pharmacol P* 32, 145–146.

Knutson, J. S., Naples, G. G., Peckham, P. H., and Keith, M. W. (2002). Electrode fracture rates and occurrences of infection and granuloma associated with percutaneous intramuscular electrodes in upper-limb functional electrical stimulation applications. *J Rehabil Res Dev* 39, 671–684.

Kuiken, T. a, Marasco, P. D., Lock, B. a, Harden, R. N., and Dewald, J. P. a (2007a). Redirection of cutaneous sensation from the hand to the chest skin of human amputees with targeted reinnervation. *Proc Natl Acad Sci USA* 104, 20061–6.

Kuiken, T. A., Miller, L. A., Lipschutz, R. D., Lock, B. A., Stubblefi, K., Marasco, P. D., Zhou, P., and Dumanian, G. A. (2007b). Targeted reinnervation for enhanced prosthetic arm function in a woman with a proximal amputation : a case study. *Lancet* 369, 371–380.

Kuiken, T., Dumanian, G., Lipschutz, R., Miller, L. A., and Stubblefield, K. (2004). The use of targeted muscle reinnervation for improved myoelectric prosthesis control in a bilateral shoulder disarticulation amputee. *Prosthet Orthot Int* 28, 245–253. Available at: http://informahealthcare.com/doi/abs/10.3109/03093640409167756.

Kuiken, T., Li, G., Lock, B. A., Lipschutz, R. D., Miller, L. A., Stubblefield, K. A., and Englehart, K. B. (2009). Targeted muscle reinnervation for real-time myoelectric control of multifunction artificial arms. *JAMA J. Am. Med. Assoc.* 301, 619–628. Available at: http://jama.ama-assn.org/content/301/6/619.short.

Kuiken, T., Lowery, M. M., and Stoykov, N. S. (2003). The effect of subcutaneous fat on myoelectric signal amplitude and cross-talk. *Prosthet. Orthot. Int.* 27, 48–54.

Kung, T. a, Bueno, R. a, Alkhalefah, G. K., Langhals, N. B., Urbanchek, M. G., and Cederna, P. S. (2013a). Innovations in prosthetic interfaces for the upper extremity. *Plast. Reconstr. Surg.* 132, 1515–23..

Kung, T. a., Cederna, P. S., Langhals, N. B., Martin, D. C., and Urbanchek, M. G. (2013b). Augmented Signal Transduction from Regenerative Peripheral Nerve Interfaces. *Plast. Reconstr. Surg.* 132, 89.

Kung, T. A., Langhals, N. B., Martin, D. C., Johnson, P. J., Cederna, P. S., and Urbanchek, M. G. (2014). Regenerative Peripheral Nerve Interface Viability and Signal Transduction with an Implanted Electrode. *Press - Plast. Reconstr. Surg.*

Kyberd, P. J., Wartenberg, C., Sandsjö, L., Jönsson, S., Gow, D., Frid, J., Almström, C., and Sperling, L. (2007). Survey of upper-extremity prosthesis users in Sweden and the United Kingdom. *J Prosthet Orthot* 19, 55–62.

Laferriere, P., Chan, A. D. C., and Lemaire, E. D. (2011). Surface electromyographic signals using a dry electrode. *IEEE Trans. Instrum. Meas.* 60, 3259–3268.

LeBlanc, M. (1985). Innovation and improvement of body-powered arm prostheses: A first step. *Clin Pros Orth* 9, 13–16. Available at: http://oandplibrary.com/cpo/pdf/1985_01_013.pdf

Lee, S. W., Wilson, K. M., Lock, B. a, and Kamper, D. G. (2011). Subject-specific myoelectric pattern classification of functional hand movements for stroke survivors. *IEEE Trans Neural Syst Rehabil Eng* 19, 558–66.

Lewis, S., Russold, M., Dietl, H., Roman, R., Cardona Audi, J. M., Hoffmann, K.-P., Abu-Saleh, L., Schroeder, D., Krautschneider, W., Westendorff, S., et al. (2013). Fully Implantable Multi-Channel Measurement System for Acquisition of Muscle Activity. *IEEE Trans Instrum Meas* 62, 1972–1981.

Li, G., Geng, Y., Tao, D., and Zhou, P. (2011). Performance of electromyography recorded using textile electrodes in classifying arm movements. in *33rd Ann Int Conf IEEE EMBS* (Boston), 4243–6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22255276.

Li, G., Schultz, A. E., and Kuiken, T. (2010). Quantifying pattern recognition-based myoelectric control of multifunctional transradial prostheses. *IEEE Trans Neural Syst Rehabil Eng* 18, 185–92. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20071269.

Liu, J., and Zhou, P. (2013). A novel myoelectric pattern recognition strategy for hand function restoration after incomplete cervical spinal cord injury. *IEEE Trans Neural Syst Rehabil Eng* 21, 96–103.

Liu, L., Liu, P., Clancy, E. A., Member, S., Scheme, E., Member, S., and Englehart, K. B. (2013). Electromyogram Whitening for Improved Classi fi cation Accuracy in Upper Limb Prosthesis Control. *IEEE Trans Neural Syst Rehabil Eng* 21, 767–774.

Lock, B. A., Englehart, K., and Hudgins, B. (2005). Real-time myoelectric control in a virtual environment to relate usability vs. accuracy. in *Proc. MyoElectric Controls/Powered Prosthetics Symposium* (Fredericton). Available at: http://dukespace.lib.duke.edu/dspace/bitstream/handle/10161/2721/Lock_01.pdf?sequence=3

De Luca, C. J., Gilmore, L. D., Bloom, L. J., Thomson, S. J., Cudworth, a L., and Glimcher, M. J. (1982). Long-term neuroelectric signal recording from severed nerves. *IEEE Trans Biomed Eng* 29, 393–403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7106789.

De Luca, C. J., Gilmore, L. D., Kuznetsov, M., and Roy, S. H. (2010). Filtering the surface EMG signal: Movement artifact and baseline noise contamination. *J. Biomech.* 43, 1573–1579. Available at: http://dx.doi.org/10.1016/j.jbiomech.2010.01.027.

Lundberg, M., Hagberg, K., and Bullington, J. (2011). My prosthesis as a part of me: a qualitative analysis of living with an osseointegrated prosthetic limb. *Prosthet Orthot Int* 35, 207–14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21697203.

Lundborg, G., Waites, A., Björkman, A., Rosén, B., and Larsson, E.-M. (2006). Functional magnetic resonance imaging shows cortical activation on sensory stimulation of an osseointegrated prosthetic thumb. *Scand J Plast Reconstr Surg Hand Surg* 40, 234–9.

Lyon, C. C., Kulkarni, J., Zimerson, E., Van Ross, E., and Beck, M. H. (2000). Skin disorders in amputees. *J Am Acad Dermatol* 42, 501–7.

Mabuchi, K. (2013). An Artificial Arm/Hand System with a Haptic Sensory Function Using Electric Stimulation of Peripheral Sensory Nerve Fibers. in *35th Ann Int Conf IEEE EMBS* (Osaka), 3130–3133.

Marasco, P. D., Kim, K., Colgate, J. E., Peshkin, M. a, and Kuiken, T. (2011). Robotic touch shifts perception of embodiment to a prosthesis in targeted reinnervation amputees. *Brain* 134, 747–58.

Matulevich, B., Loeb, G. E., and Fishel, J. A. (2013). Utility of Contact Detection Reflexes in Prosthetic Hand Control. in *IEEE/RSJ Int Conf Intelligent Robots and Systems* (Tokyo), 4741–4746.

McCool, P., and Chatlani, N. (2012). 1-D Local Binary Patterns for onset detection of myoelectric signals. in *20th European Signal Processing Conference (EUSIPCO 2012)* (Bucharest), 499–503. Available at: http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=6334024

McDonnall, D., Hiatt, S., Smith, C., and Guillory, K. S. (2012). Implantable multichannel wireless electromyography for prosthesis control. in *34th Ann Int Conf IEEE EMBS* (San Diego), 1350–3. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23366149.

Meier, K., Nikolajsen, L., Flink, M., Simonsen, R., Milidou, I., Jensen, T. S., and Sorensen, J. C. (2013). The aarhus neuromodulation database. *Neuromodulation* 16, 506–13.

Memberg, W. D., Polasek, K. H., Hart, R. L., Bryden, A. M., Kilgore, K. L., Nemunaitis, G. a, Hoyen, H. a, Keith, M. W., and Kirsch, R. F. (2014). An Implanted Neuroprosthesis for Restoring Arm and Hand Function in People with High Level Tetraplegia. *Arch Phys Med Rehabil.*

Merletti, R., Botter, A., Troiano, A., Merlo, E., and Minetto, M. A. (2009). Technology and instrumentation for detection and conditioning of the surface electromyographic signal: state of the art. *Clin. Biomech.* 24, 122–134.

Merrill, D. R., Lockhart, J., Troyk, P. R., Weir, R. F., and Hankin, D. L. (2011). Development of an implantable myoelectric sensor for advanced prosthesis control. *Artif Organs* 35, 249–252.

Metting Van Rijn, A. C., Peper, A., and Grimbergen, C. A. (1990). High-quality recording of bioelectric events. *Med Biol Eng Comput* 28, 389–397. Available at: http://link.springer.com/article/10.1007/BF02441961.

Micera, S., Citi, L., Rigosa, J., Carpaneto, J., Raspopovic, S., Di Pino, G., Rossini, L., Yoshida, K., Denaro, L., Dario, P., et al. (2010). Decoding information from neural signals recorded using intraneural electrodes: toward the development of a neurocontrolled hand prosthesis. *Proc. IEEE* 98, 407–417. Available at: http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=5415651.

Mooney, V., and Predecki, P. (1971). Skeletal extension of limb prosthetic attachments–problems in tissue reaction. *J Biomed Mater Res Symp.* 2, 143–159. Available at: http://onlinelibrary.wiley.com/doi/10.1002/jbm.820050612/abstract.

Muceli, S., and Farina, D. (2012). Simultaneous and Proportional Estimation of Hand Kinematics From EMG During Mirrored Movements at Multiple Degrees of Freedom. *IEEE Trans Neural Syst Rehabil Eng* 20, 371–8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22180516.

Muceli, S., Jiang, N., and Farina, D. (2013). Extracting Signals Robust to Electrode Number and Shift for Online Simultaneous and Proportional Myoelectric Control by Factorization Algorithms. *IEEE Trans Neural Syst Rehabil Eng* 22, 623–633.

Nashold, B. S., Goldner, J. L., Mullen, J. B., and Bright, D. S. (1982). Long-term pain control by direct peripheral-nerve stimulation The of Joint Long-Term by Direct. *J Bone Jt. Surg Am* 64, 1–10.

Navarro, X., Krueger, T. B., Lago, N., Micera, S., Stieglitz, T., and Dario, P. (2005). A critical review of interfaces with the peripheral nervous system for the control of neuroprostheses and hybrid bionic systems. *J Peripher Nerv Syst* 10, 229–58.

Nebergall, A., Bragdon, C., Antonellis, A., Kärrholm, J., Brånemark, R., and Malchau, H. (2012). Stable fixation of an osseointegated implant system for above-the-knee amputees: titel RSA and radiographic evaluation of migration and bone remodeling in 55 cases. *Acta Orthop.* 83, 121–8.

Nyström, B., and Hagbarth, K. E. (1981). Microelectrode recordings from transected nerves in amputees with phantom limb pain. *Neurosci. Lett.* 27, 211–6.

Olausson, H., Wessberg, J., Morrison, I., McGlone, F., and Vallbo, A. (2010). The neurophysiology of unmyelinated tactile afferents. *Neurosci. Biobehav. Rev.* 34, 185–91.

Ortiz Catalan, M. J. (2010). Biosignals Acquisition and Pattern Recognition for Robotic Prostheses. *Thesis for the degree of Master in Science in Complex Adaptive System*, Deparment of Applied Physics, Chalmers University of Technology.

Ortiz-Catalan, M. (2010). Osseointegration and Neural Interfaces. presentation at the *3rd International Conference on Advances in Orthopaedic Osseointegration* (Gothenburg), Sep 2–4.

Ortiz-Catalan, M., Brånemark, R., and Håkansson, B. (2012). Biologically Inspired Algorithms Applied to Prosthetic Control. in *Proceedings of the IASTED International Conference, Biomedical Engineering* (Innsbruck), 7–15.

Ortiz-Catalan, M., Brånemark, R., and Håkansson, B. (2013a). Evaluation of classifier topologies for the real-time classification of simultaneous limb motions. in *35th Ann Int Conf IEEE EMBS* (Osaka).

Ortiz-Catalan, M., Håkansson, B., and Brånemark, R. (2013b). Real-time classification of simultaneous hand and wrist motions using Artificial Neural Networks with variable threshold outputs. in *Proceedings of the XXXIV International Conference on Artificial Neural Networks (ICANN)* (Amsterdam), 1159–1164. Available at: http://publications.lib.chalmers.se/records/fulltext/176132/local_176132.pdf.

Ortiz-Catalan, M., Sander, N., Kristoffersen, M. B., Håkansson, B., and Brånemark, R. (2014). Treatment of phantom limb pain (PLP) based on augmented reality and gaming controlled by myoelectric pattern recognition: a case study of a chronic PLP. *Front. Neurosci.* 8. Available at: http://journal.frontiersin.org/Journal/10.3389/fnins.2014.00024/abstract.

Oskoei, M. A., and Hu, H. (2008). Support vector machine-based classification scheme for myoelectric control applied to upper limb. *IEEE Trans Biomed Eng* 55, 1956–65.

Parker, P., Englehart, K., and Hudgins, B. (2004). "Control of powered upper limb prstheses," in *Electromyography: physiology, engineering, and noninvasive applications*, eds. R. Merletti and P. Parker (Wiley-IEEE), 453–475.

Parker, P., and Scott, R. N. (1986). Myoelectric Control of Prostheses. *Crit Rev Biomed Eng* 13, 283–310.

Pasquina, P.F., Evangelista, M., Carvalho, A.J., Lockhart, J., Griffin, S., Nanos, G., McKey, P., Hansen, M., Miller, M., Murphy, I., and Hankin, D (under review). Frist-in-man demonstration of fully implanted myoelectric sensors for control of an advanced electromechanical arm by transradial amputees. *J Neurosci Meth*.

Peckham, P. H., Keith, M. W., Kilgore, K. L., Grill, J. H., Wuolle, K. S., Thrope, G. B., Gorman, P., Hobby, J., Mulcahey, M. J., Carroll, S., et al. (2001). Efficacy of an implanted neuroprosthesis for restoring hand grasp in tetraplegia: a multicenter study. *Arch Phys Med Rehabil* 82, 1380–8.

Pezzin, L. E., Dillingham, T. R., MacKenzie, E. J., Ephraim, P., and Rossbach, P. (2004). Use and satisfaction with prosthetic limb devices and related services. *Arch Phys Med Rehabil* 85, 723–729.

Pezzin, L. I., Dillingham, T. R., and MacKenzie, E. J. (2000). Rehabilitation and the long-term outcomes of persons with trauma-related amputations. *Arch Phys Med Rehabil* 81, 292–300.

Pistohl, T., Cipriani, C., Jackson, A., and Nazarpour, K. (2013). Abstract and Proportional Myoelectric Control for Multi-Fingered Hand Prostheses. *Ann. Biomed. Eng.* 41, 2687–2698.

Pitkin, M. (2013). Design features of implants for direct skeletal attachment of limb prostheses. *J Biomed Mater Res Part A* 101A, 3339–48.

Pitkin, M., Cassidy, C., Muppavarapu, R., and Edell, D. (2012). Recording of electric signal passing through a pylon in direct skeletal attachment of leg prostheses with neuromuscular control. *IEEE Trans Biomed Eng* 59, 1349–53.

Polasek, K. H., Hoyen, H. A., Keith, M. W., Kirsch, R. F., and Tyler, D. J. (2009). Stimulation Stability and Selectivity of Chronically Implanted Multicontact Nerve Cuff Electrodes in the Human Upper Extremity. *IEEE Trans Neural Syst Rehabil Eng* 17, 428–437.

Pulliam, C. L., Lambrecht, J. M., and Kirsch, R. F. (2011). Electromyogram-based neural network control of transhumeral prostheses. *J Rehabil Res Dev* 48, 739–754. Available at: http://www.rehab.research.va.gov/jour/11/486/pdf/pulliam486.pdf [Accessed April 29, 2014].

Rasool, G., Iqbal, K., Bouaynaya, N., and White, G. (2013). Neural drive estimation using the hypothesis of muscle synergies and the state-constrained Kalman filter. in *6th International IEEE/EMBS Conference on Neural Engineering (NER)* (San Diego), 802–805. Available at: http://ieeexplore.ieee.org/lpdocs/epic03/wrapper.htm?arnumber=6696056.

Raspopovic, S., Capogrosso, M., Petrini, F. M., Bonizzato, M., Rigosa, J., Di Pino, G., Carpaneto, J., Controzzi, M., Boretius, T., Fernandez, E., et al. (2014). Restoring natural sensory feedback in real-time bidirectional hand prostheses. *Sci. Transl. Med.* 6, 222ra19.

Von Recum, A. F. (1984). Applications and failure modes of percutaneous devices: a review. *J Biomed Mater Res* 18, 323–36. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6234317.

Reiter, R. (1948). Eine neu elecktrokunstand. *Grenzgebeiter der Med.* 1, 133–135.

Resnik, L., Etter, K., Klinger, S. L., and Kambe, C. (2011). Using virtual reality environment to facilitate training with advanced upper-limb prosthesis. *J Rehabil Res Dev* 48, 707–718. Available at: http://www.rehab.research.va.gov/jour/11/486/pdf/resnik2486.pdf.

Ridder, D. De, Vanneste, S., Engineer, N. D., and Kilgard, M. P. (2013). Safety and Efficacy of Vagus Nerve Stimulation Paired With Tones for the Treatment of Tinnitus : A Case Series. *Neuromodulation Technol. Neural Interface* 17, 170–9.

Roche, A. D., Rehbaum, H., Farina, D., and Aszmann, O. C. (2014). Prosthetic Myoelectric Control Strategies : A Clinical Perspective. *Curr Surg Rep* 2.

Rouse, E. J., Nahlik, D. C., Peshkin, M. a, and Kuiken, T. (2011). Development of a model osseo-magnetic link for intuitive rotational control of upper-limb prostheses. *IEEE Trans Neural Syst Rehabil Eng* 19, 213–20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21193382.

Saridis, G. N., and Gootee, T. P. (1982). EMG pattern analysis and classification for a prosthetic arm. *IEEE Trans Biomed Eng* 29, 403–12.

Saunders, I., and Vijayakumar, S. (2011). The role of feed-forward and feedback processes for closed-loop prosthesis control. *J Neuroengineering Rehabil* 8, 60.

Scheme, E., and Englehart, K. (2013a). Training Strategies for Mitigating the Effect of Proportional Control on Classification in Pattern Recognition–Based Myoelectric Control. *J Prosthet Orthot* 25, 76–83.

Scheme, E. J., and Englehart, K. (2011). Electromyogram pattern recognition for control of powered upper-limb prostheses: State of the art and challenges for clinical use. *J Rehabil Res Dev* 48, 643. Available at: http://www.rehab.research.va.gov/jour/11/486/pdf/scheme486.pdf.

Scheme, E. J., and Englehart, K. B. (2013b). Validation of a Selective Ensemble-Based Classification Scheme for Myoelectric Control Using a Three Dimensional Fitts' Law Test. *IEEE Trans Neural Syst Rehabil Eng* 21, 616–623.

Scheme, E. J., Englehart, K. B., and Hudgins, B. S. (2011). Selective classification for improved robustness of myoelectric control under nonideal conditions. *IEEE Trans Biomed Eng* 58, 1698–705.

Scheme, E. J., Hudgins, B. S., and Englehart, K. B. (2013). Confidence-based rejection for improved pattern recognition myoelectric control. *IEEE Trans Biomed Eng* 60, 1563–70.

Scheme, E., Member, S., Lock, B., Hargrove, L., Hill, W., Kuruganti, U., Englehart, K., and Member, S. (2014). Motion Normalized Proportional Control for Improved Pattern Recognition Based Myoelectric Control. *IEEE Trans Neural Syst Rehabil Eng* 22, 149–157.

Schultz, A. E., and Kuiken, T. a (2011). Neural interfaces for control of upper limb prostheses: the state of the art and future possibilities. *PM R* 3, 55–67.

Schwartz, A. R., Bennett, M. L., Smith, P. L., De Backer, W., Hedner, J., Boudewyns, A., Van de Heyning, P., Ejnell, H., Hochban, W., Knaack, L., et al. (2001). Therapeutic electrical stimulation of the hypoglossal nerve in obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg* 127, 1216–23.

Sebelius, F. C. P., Rosén, B. N., and Lundborg, G. N. (2005). Refined myoelectric control in below-elbow amputees using artificial neural networks and a data glove. *J. Hand Surg. Am.* 30, 780–9.

Segil, J., and Weir, R. (2014). Design and Validation of a Morphing Myoelectric Hand Posture Controller based on Principal Component Analysis of Human Grasping. *IEEE Trans Neural Syst Rehabil Eng* 22, 249–257.

Sensinger, J. W., Lock, B. a, and Kuiken, T. (2009). Adaptive pattern recognition of myoelectric signals: exploration of conceptual framework and practical algorithms. *IEEE Trans Neural Syst Rehabil Eng* 17, 270–8.

Shah, S. R., Tatara, A. M., Souza, R. N. D., Mikos, A. G., and Kasper, F. K. (2013). Evolving strategies for preventing biofilm on implantable materials. *Mater. Today* 16, 177–182.

Sharma, A., Rieth, L., Tathireddy, P., Harrison, R., Oppermann, H., Klein, M., Töpper, M., Jung, E., Normann, R., Clark, G., et al. (2011). Long term in vitro functional stability and recording longevity of fully integrated wireless neural interfaces based on the Utah Slant Electrode Array. *J. Neural Eng.* 8, 045004.

Shenoy, P., Miller, K. J., Crawford, B., and Rao, R. N. (2008). Online electromyographic control of a robotic prosthesis. *IEEE Trans Biomed Eng* 55, 1128–35.

Sherman, E. D. (1964). a Russian Bioelectric-Controlled Prosthesis: Report of a Research Team From the Rehabilitation Institute of Montreal. *Can. Med. Assoc. J.* 91, 1268–70.

Shibanoki, T., Shima, K., Tsuji, T., Otsuka, A., and Chin, T. (2013). A Quasi-Optimal Channel Selection Method for Bioelectric Signal Classification Using a Partial Kullback-Leibler Information Measure. *IEEE Trans Biomed Eng* 60, 853–861.

Sikes, J. M., and Newmark, P. a. (2013). Restoration of anterior regeneration in a planarian with limited regenerative ability. *Nature* 0, 1–5.

Simon, A. M., Hargrove, L. J., Lock, B. A., and Kuiken, T. (2011a). A decision-based velocity ramp for minimizing the effect of misclassifications during real-time pattern recognition control. *IEEE Trans Biomed Eng* 58, 2360–2368.

Simon, A. M., Hargrove, L. J., Lock, B. A., and Kuiken, T. (2011b). Target Achievement Control Test: Evaluating real-time myoelectric pattern-recognition control of multifunctional upper-limb prostheses. *J Rehabil Res Dev* 48, 619–628.

Simon, A. M., Stern, K., and Hargrove, L. J. (2011c). A Comparison of Proportional Control Methods for Pattern Recognition Control. in *Proc. 33rd Annu. Int. Conf. IEEE EMBS* (Boston), 3354–3357.

Snik, A. F. M., Mylanus, E. A. M., Proops, D. W., Wolfaardt, J. F., Hodgetts, W. E., Somers, T., Niparko, J. K., Wazen, J. J., Sterkers, O., Cremers, C. W. R. J., et al. (2005). Consensus statements on the BAHA system: where do we stand at present? in *Ann Otol Rhinol Laryngol Suppl.*, 2–12.

Stein, R. B., Charles, D., Hoffer, J. a, Arsenault, J., Davis, L. a, Moorman, S., and Moss, B. (1980). New approaches for the control of powered prostheses particularly by high-level amputees. *Bull. Prosthet. Res.* 17, 51–62. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7236946.

Sullivan, J., Uden, M., Robinson, K. P., and Sooriakumaran, S. (2003). Rehabilitation of the trans-femoral amputee with an osseointegrated prosthesis: the United Kingdom experience. *Prosthet Orthot Int* 27, 114–20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14571941.

Tahry, R. El, Raedt, R., Mollet, L., De Herdt, V., Wyckhuys, T., Wyckuys, T., Van Dycke, A., Meurs, A., Dewaele, F., Van Roost, D., et al. (2010). A novel implantable vagus nerve stimulation system (ADNS-300) for combined stimulation and recording of the vagus nerve: pilot trial at Ghent University Hospital. *Epilepsy Res.* 92, 231–9.

Tan, D., Schiefer, M., Keith, M. W., Anderson, R., and Tyler, D. J. (2013). Stability and selectivity of a chronic , multi-contact cuff electrode for sensory stimulation in a human amputee. in *6th Ann Int IEEE/EMBS Conf Neural Eng* (San Diego), 859–862.

Thomsson, M., and Larsson Wexell, C. (2013). A 5-year retrospective case series evaluating Brånemark Integration BioHelix (^{TM}) dental implants placed in a private practice by a specialist. *Acta Odontol. Scand.* 71, 1195–9.

Tillander, J., Hagberg, K., Hagberg, L., and Brånemark, R. (2010). Osseointegrated titanium implants for limb prostheses attachments: infectious complications. *Clin Orthop Relat Res* 468, 2781–8.

Tkach, D., Huang, H., and Kuiken, T. (2010). Study of stability of time-domain features for electromyographic pattern recognition. *J Neuroengineering Rehabil* 7, 21.

Tkach, D., Young, A., Smith, L., Rouse, E., and Hargrove, L. (2014). Real-Time and Offline Performance of Pattern Recognition Myoelectric Control Using a Generic Electrode Grid With Targeted Muscle Reinnervation Patients. *IEEE Trans Neural Syst Rehabil Eng* (in press).

Tranberg, R., Zügner, R., and Kärrholm, J. (2011). Improvements in hip- and pelvic motion for patients with osseointegrated trans-femoral prostheses. *Gait Posture* 33, 165–8.

Tsoumakas, G., and Katakis, I. (2007). Multi-Label Classification: An Overview. *Int. J. Data Warehous. Min.* 3, 1–13.

Urbanchek, M. G., Baghmanli, W., Baghmanli, Z., Sugg, K., and Cederna, P. S. (2011). Long-term stability of regenerative peripheral nerve interfaces (RPNI). *Plast Reconstr Surg* 128, 88–89.

Waters, R. L., McNeal, D., and Perry, J. (1975). Experimental correction of footdrop by electrical stimulation of the peroneal nerve. *J Bone Jt. Surg* 57, 1047–54.

Waters, R. L., McNeal, D. R., Faloon, W., Clifford, B., and California, D. (1985). Functional electrical stimulation of the peroneal nerve for hemiplegia. Long-term clinical follow-up. *J Bone Jt. Surg Am* 67, 792–3.

Weber, D. J., Friesen, R., and Miller, L. E. (2012). Interfacing the somatosensory system to restore touch and proprioception: essential considerations. *J. Mot. Behav.* 44, 403–18.

Weir, R. F., Troyk, P. R., DeMichele, G. a, Kerns, D. a, Schorsch, J. F., and Maas, H. (2009). Implantable myoelectric sensors (IMESs) for intramuscular electromyogram recording. *IEEE Trans Biomed Eng* 56, 159–71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19224729.

Veraart, C., Raftopoulos, C., Mortimer, J. T., Delbeke, J., Pins, D., Michaux, G., Vanlierde, A., Parrini, S., and Wanet-Defalque, M. C. (1998). Visual sensations produced by optic nerve stimulation using an implanted self-sizing spiral cuff electrode. *Brain Res.* 813, 181–6.

Wessberg, J., Stambaugh, C. R., Kralik, J. D., Beck, P. D., Laubach, M., Chapin, J. K., Kim, J., Biggs, S. J., Srinivasan, M. a, and Nicolelis, M. a (2000). Real-time prediction of hand trajectory by ensembles of cortical neurons in primates. *Nature* 408, 361–5.

WHO (2002). Towards a Common Language for Functioning , Disability and Health - ICF. *ICF*. Available at http://www.who.int/entity/classifications/icf/icfbeginnersguide.pdf?ua=1

Wirta, R. W., Taylor, D. R., and Finley, F. R. (1978). Pattern-recognition arm prosthesis: a historical perspective-a final report. *Bull. Prosthet. Res.* Fall, 8–35.

Witteveen, H. J. B., Droog, E. A., Rietman, J. S., and Veltink, P. H. (2012). Vibro- and electrotactile user feedback on hand opening for myoelectric forearm prostheses. *IEEE Trans Biomed Eng* 59, 2219–2226.

Yatsenko, D., McDonnall, D., and Guillory, K. S. (2007). Simultaneous, proportional, multi-axis prosthesis control using multichannel surface EMG. in *29th Ann Int Conf IEEE EMBS* (Lyon), 6134–7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18003415.

Yerneni, S., Dhaher, Y., and Kuiken, T. a (2012). A computational model for stress reduction at the skin-implant interface of osseointegrated prostheses. *J Biomed Mater Res Part A* 100, 911–7.

Young, A. J., Hargrove, L. J., and Kuiken, T. (2012). Improving Myoelectric Pattern Recognition Robustness to Electrode Shift by Changing Interelectrode Distance and Electrode Configuration. *IEEE Trans Biomed Eng* 59, 645–652.

Young, A. J., Hargrove, L. J., and Kuiken, T. (2011). The effects of electrode size and orientation on the sensitivity of myoelectric pattern recognition systems to electrode shift. *IEEE Trans Biomed Eng* 58, 2537–44.

Young, A. J., Smith, L. H., Rouse, E. J., and Hargrove, L. J. (2014). A comparison of the real-time controllability of pattern recognition to conventional myoelectric control for discrete and simultaneous movements. *J Neuroengineering Rehabil* 11, 5.

Young, A. J., Smith, L. H., Rouse, E. J., and Hargrove, L. J. (2013). Classification of simultaneous movements using surface EMG pattern recognition. *IEEE Trans Biomed Eng* 60, 1250–1258.

Zaborowska, M., Welch, K., Brånemark, R., Khalilpour, P., Engqvist, H., and Thomsen, P. (2014). Bacteria-material surface interactions: methodological development for the assessment of implant surface induced antibacterial effects. *J Biomed Mater Res Part B* (in press).

Ziegler-Graham, K., MacKenzie, E. J., Ephraim, P. L., Travison, T. G., and Brookmeyer, R. (2008). Estimating the prevalence of limb loss in the United States: 2005 to 2050. *Arch. Phys. Med. Rehabil.* 89, 422–9.